

10620X2126102

Tumor treating fields: concept, evidence and future

- radiosensitivity of squamous carcinoma cell lines of the head and neck, *Cancer Res* 1996;56(22):5198-204
25. Novello S, Le Chevalier T. Use of chequaradiotherapy in locally advanced non-small cell lung cancer. *Eur J Cancer* 2002;38(2):292-9
 26. Chay H, Kim DW. Chemotherapy and irradiation interaction. *Semin Oncol* 2005;30(4 Suppl 9):9-10
 27. Stewart TJ, Greenleach KM, Lusak MB, Abrams SI. Immunological responses can have both pro- and antitumour effects: implications for immunotherapy. *Expert Rev Mol Med* 2007;9(4):1-20
 28. Selaburg M, Elson E, Fild Y, Rochlitz C. A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. *Onkologie* 2008;11(7):362-5
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 30. Sjostrom S, Andersson U, Liu Y, et al. Genetic variations in EGFR and EGFR and glioblastoma outcome. *Neuro Oncol* 2010;12(8):815-21
 31. Lee W, Jiang Z, Liu J, et al. The mutation spectrum revealed by paired genome sequences from a lung cancer patient. *Nature* 2010;463(7297):470-7

Affiliation

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Brauerstrasse 19,

8400 Winterthur, Switzerland

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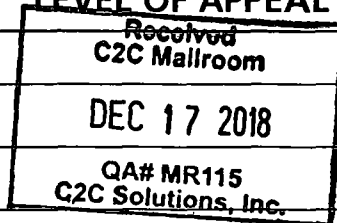
²NovoCure Ltd,

Matam Advanced Technology Centre,

31905, Haifa, Israel

MEDICARE RECONSIDERATION REQUEST FORM — 2ND LEVEL OF APPEAL

1. Beneficiary's name: Anniken S. Prosser
2. Medicare number: 389044857A
3. Item or service you wish to appeal: E0766 KF RR
4. Date the service or item was received: 01/16/2018, 02/16/2018, 03/16/2018, 04/16/2018
5. Date of the redetermination notice (please include a copy of the notice with this request):
(If you received your redetermination notice more than 180 days ago, include your reason for the late filing.)
July 10, 2018



5a. Name of the Medicare contractor that made the redetermination (not required if copy of notice attached):

5b. Does this appeal involve an overpayment? ☐ Yes ☒ No
(for providers and suppliers only)

6. I do not agree with the redetermination decision on my claim because:

This is a FDA approved treatment for recurrent glioblastoma multiforme. I have attached the physician order, FDA approval letter, NCCN Guidelines, a clinical overview of the device and the patient's medical record.

7. Additional information Medicare should consider:

Novocure is an accredited CMS DMEPOS supplier by the Accreditation Commission for Healthcare and Novocure is a CMS supplier for Durable Medical Equipment as of March 1, 2013 completed the Medicare application process and received their PTAN on 3/1/13. On 7/26/13, Novocure received a letter from CMS stating the NovoTTF-100A System falls within the DME benefit category. Please see attached.

8. ☒ I have evidence to submit. Please attach the evidence to this form or attach a statement explaining what you intend to submit and when you intend to submit it. You may also submit additional evidence at a later time, but all evidence must be received prior to the issuance of the reconsideration.
- ☐ I do not have evidence to submit.

9. Person appealing: ☐ Beneficiary ☒ Provider/Supplier ☐ Representative

10. Name, address, and telephone number of person appealing: Sandy Rice (603) 617-4768
195 Commerce Way Portsmouth, NH 03801

11. Signature of person appealing: Sandy Rice

12. Date signed: 12-11-2018

PRIVACY ACT STATEMENT: The legal authority for the collection of information on this form is authorized by section 1869 (a)(3) of the Social Security Act. The information provided will be used to further document your appeal. Submission of the information requested on this form is voluntary, but failure to provide all or any part of the requested information may affect the determination of your appeal. Information you furnish on this form may be disclosed by the Centers for Medicare and Medicaid Services to another person or government agency only with respect to the Medicare Program and to comply with Federal laws requiring or permitting the disclosure of information or the exchange of information between the Department of Health and Human Services and other agencies. Additional information about these disclosures can be found in the system of records notice for system no. 09-70-0566, as amended, available at 71 Fed. Reg. 54489 (2006) or at <http://www.cms.gov/PrivacyActSystemofRecords/downloads/0566.pdf>

Form CM5-20033 (12/10)

Jurisdiction B
P.O. Box 20007
Nashville, TN 37202

MEDICARE DME

July 10, 2018

DoJ

Novocure Inc
195 Commerce Way
Portsmouth, NH 03801-9999

11-7-18

Beneficiary Name: Anniken S. Prosser
HICN: XXX-XX-4857A
Appeal Number: 18157000135
Date of Service: January 16, 2018 through April 16, 2018
Type of Service: Tumor Treatment Field Therapy (TTFT)
Supplier: Novocure Inc

Dear Novocure Inc:

Please note that if you did not request this appeal, you are receiving this letter as a copy.

DECISION

This letter is to inform you of an **UNFAVORABLE** Medicare Appeal decision. Based on a new and independent review of the claims at issue, we find the electrical stimulation device is not covered by Medicare. The beneficiary is not responsible for payment. If you disagree with this decision, you may appeal to the Qualified Independent Contractor (QIC), C2C Innovative Solutions, Inc., as explained in the Future Appeal Rights section of this letter.

SUMMARY OF FACTS

Claims were submitted for the electrical stimulation device for dates of service January 16, 2018 through April 16, 2018. The claims were initially denied on February 20, 2018, because Medicare guidelines were not met. A redetermination request was received on June 6, 2018. The redetermination case included the following documentation: medical and administrative records.

APPLICABLE MEDICARE GUIDELINES AND RULES

The Medicare coverage policies are set forth below for the item or service in question. These rules are available at www.cmsmedicare.com.

- CMS Medicare Coverage Database, Local Coverage Determination (LCD) L34823-Tumor Treatment Field Therapy (TTFT)
- Social Security Act, Section 1879, Limitation on Liability

EXPLANATION OF DECISION

18157000135

RECONSIDERATION REQUEST FORM Redetermination Number: 18157000135
Contractor #: 17013, CGS, DME MAC Jurisdiction B

Directions: If you wish to appeal this decision, please fill out the information below and mail this form to the address below. At a minimum, you must complete/include information for items 1, 2a, 6, 7, 11, & 12, but to help us serve you better, please include a copy of the redetermination notice with your request.

C2C Solutions, Inc.
 Attn: DME Qualified Independent Contractor (QIC)
 P. O. Box 44013
 Jacksonville, FL 32231-4013

1. Name of Beneficiary: Anniken S. Prosser
- 2a. Medicare Number: 389044857A
- 2b. Claim Number (ICN/DCN, if available): 18157000135
3. Provider/Supplier Name and Number (PTAN): Novocure 6723630001
4. Person Appealing ☐ Beneficiary ☒ Provider ☐ Representative of Service
5. Address of the Person Appealing: 195 Commerce Way, Portsmouth, NH
- 5a. Telephone Number of the Person Appealing: 603-617-4768
- 5b. Email Address of the Person Appealing: SRice@novocure.com
6. Item or service you wish to appeal: E0766 KF RR
7. Date of Service: From 1/16/2018 To 4/16/2018
8. Does this appeal involve an overpayment? ☐ Yes ☒ No
**Please include a copy of the demand letter with your request.*
9. Why do you disagree? Or what are your reasons for your appeal? (Attach additional pages, if necessary.) Please see attached

10. You may also include any supporting material to assist your appeal. Examples of supporting materials include:

- ☒ Medical Records ☒ Office Records/Progress Notes ☒ Copy of the Claim
☒ Treatment Plan ☐ Certificate of Medical Necessity

11. Printed Name of Person Appealing: Sandy Rice
12. Signature of Person Appealing: Sandy Rice
 Date: 12-11-2018
 Contractor Number: 17013, CGS, DME MAC Jurisdiction B

MEDICARE DME Redetermination Request Form

Supplier Information

Supplier Name Novocure INCPTAN 6723630001 NPI 1255617569Tax ID 205063536Address 195 Commerce WayCity PortsmouthState NH Zip Code 03801Phone Number (603) 617-4768☐ Jurisdiction A - Noridian Healthcare Solutions☒ Jurisdiction B - CGS☐ Jurisdiction C - CGS☐ Jurisdiction D - Noridian Healthcare Solutions

Beneficiary Information

Patient Name Anniken S. ProsserMedicare Number 389044857AState WisconsinPhone Number (920)257-3574Requestor's Name/Supplier Contact Name Sandy Rice

Requestor's Signature (required)

Sandy Rice

Date

06-05-2018

Overpayment Appeal ☐ Yes If yes, who requested overpayment: ☐ Medical Review ☐ ZPIC/PSC
☐ CERT ☐ Recovery Auditor

Date of Service	HCPCS & Modifiers	CCN	Date of Initial Determination
01/16/2018	E0766 KF RR	18045802101000	02/20/2018
02/16/2018	E0766 KF RR	18050808224000	02/23/2018
03/16/2018	E0766 KF RR	18078813409000	03/23/2018
04/16/2018	E0766 KF RR	18107803853000	04/23/2018

Suggested Documentation Check List: ☒ Medicare Remittance Advice ☒ CMN/DIF/Physician's Written Order
☐ ABN ☒ Medical Documentation

Reasons/Rationale - The submission of this redetermination is in regards to the denial code received: (CO-50)-"These are non-covered services because this is not deemed a 'medical necessity' by the payer." Novocure has been FDA approved since April 2011. Please see attached documentation for review.

Fax Numbers

Noridian Healthcare Solutions - JA 1-701-277-7855
 CGS Administrators, LLC - JB 1-615-660-5976
 CGS Administrators, LLC - JC 1-615-782-4630
 Noridian Healthcare Solutions - JD 1-701-277-7886



Change Healthcare ERA Check 1 of 1		EFT/Check #: 09180510044		EFT/Check Date: 02/20/2018		EFT/Check Amount: \$.00		Payment Type: NON		
		Payer Name: CGS - DME MAC JURISDICTION B				CH Payer Id: MR031		CH Process Date: 02/21/2018		
		Provider Name: NOVOCURE INC		Tax Id: 205063536		NPI: 1255617569		Other Payee Id:		
		Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999				Addl. Payee Id: 1255617569		Total PLB Adj Amt: 21000		
Service Dates: 01/16/2018		Processing Status: 4 - Denied								
Payer Claim # / Medicare ICN #: 18045802101000		CH Claim Trace Id: 044209775763659		Place Of Service:		Total Adjustment Amount: \$.00				
Charge: \$ 21,000.00		Paid: \$.00		Patient Responsibility: \$ -		Deductible: \$ -				
Co-Insurance: \$ -		Co-Pay: \$ -		Other/Crossover Insurance:						
Remark Codes:	MA13	Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07)								
	MA01	Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07)								
	M25	The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10)								
	N115	This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/mcd, or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10)								
PATIENT - SUBSCRIBER INFORMATION										
Patient Name: PROSSER, ANNIKEN S				Patient Id: 389044857A		Patient Control Number: 0001012479				
Corrected Patient/Subscriber Name:										
Subscriber Name:				Subscriber Id:		Group/Policy Id:				
Other Subscr. Name:				Other Subscriber Id:		Group/Policy Id:				
REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL										
Svc Line #	Service Date	Proc Code - Units Modifiers	Charge \$	Allowed \$	Not Allowed \$	Deductible \$	Co-Ins \$	Co-Pay \$	Late Filing Red. \$	Paid \$
1	01/16/2018	E0766 - 0 KF, RR	21,000.00	.00	.00	-	-	-	-	-
SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES										
Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount \$				
1	3	CO	Contractual Obligations	50	These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present. Start: 01/01/1995 Last Modified: 07/01/2017	21,000.00				
Claim 1 of 1					Page 1 of 1					

Change Healthcare ERA Check 1 of 1		EFT/Check #: 09180540034	EFT/Check Date: 02/23/2018	EFT/Check Amount: \$.00	Payment Type: NON					
		Payer Name: CGS - DME MAC JURISDICTION B		CH Payer Id: MR031	CH Process Date: 02/26/2018					
		Provider Name: NOVOCURE INC	Tax Id: 205063536	NPI: 1255617569	Other Payee Id:					
		Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999		Addl. Payee Id: 1255617569	Total PLB Adj Amt: 21000					
Service Dates: 02/16/2018		Processing Status: 4 - Denied								
Payer Claim # / Medicare ICN #: 18050808224000		CH Claim Trace Id: 047211576398656	Place Of Service:	Total Adjustment Amount: \$.00						
Charge: \$ 21,000.00		Paid: \$.00	Patient Responsibility: \$ -	Deductible: \$ -						
Co-Insurance: \$ -		Co-Pay: \$ -	Other/Crossover Insurance:							
Remark Codes:	MA13	Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07)								
	MA01	Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07)								
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PATIENT - SUBSCRIBER INFORMATION										
Patient Name: PROSSER, ANNIKEN S		Patient Id: 389044857A	Patient Control Number: 0001012479							
Corrected Patient/Subscriber Name:										
Subscriber Name:		Subscriber Id:	Group/Policy Id:							
Other Subscr. Name:		Other Subscriber Id:	Group/Policy Id:							
REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL										
Svc Line #	Service Date	Proc Code - Units Modifiers	Charge \$	Allowed \$	Not Allowed \$	Deductible \$	Co-Ins \$	Co-Pay \$	Late Filing Red. \$	Paid \$
1	02/16/2018	E0766 - 0 KF, RR	21,000.00	.00	00	-	-	-	-	-
SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES										
Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount \$				
1	3	CO	Contractual Obligations	50	These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present. Start: 01/01/1995 Last Modified: 07/01/2017	21,000.00				
Claim 1 of 1				Page 1 of 1						

Change Healthcare ERA Check 1 of 1		EFT/Check #: 09180820023	EFT/Check Date: 03/23/2018	EFT/Check Amount: \$.00	Payment Type: NON					
		Payer Name: CGS - DME MAC JURISDICTION B		CH Payer Id: MR031	CH Process Date: 03/26/2018					
		Provider Name: NOVOCURE INC	Tax Id: 205063536	NPI: 1255617569	Other Payee Id:					
		Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999		Addl. Payee Id: 1255617569	Total PLB Adj Amt: 21000					
Service Dates: 03/16/2018		Processing Status: 4 - Denied								
Payer Claim # / Medicare ICN #: 18078813409000		CH Claim Trace Id: 075224952936657	Place Of Service:	Total Adjustment Amount: \$.00						
Charge: \$ 21,000.00		Paid: \$.00	Patient Responsibility: \$ -	Deductible: \$ -						
Co-Insurance: \$ -		Co-Pay: \$ -	Other/Crossover Insurance:							
Remark Codes:	MA13	Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07)								
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Patient Name: PROSSER, ANNIKEN S		Patient Id: 389044857A	Patient Control Number: 0001012479							
Corrected Patient/Subscriber Name:										
Subscriber Name:		Subscriber Id:	Group/Policy Id:							
Other Subscr. Name:		Other Subscriber Id:	Group/Policy Id:							
REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL										
Svc Line #	Service Date	Proc Code - Units Modifiers	Charge \$	Allowed \$	Not Allowed \$	Deductible \$	Co-Ins \$	Co-Pay \$	Late Filing Red. \$	Paid \$
1	03/16/2018	E0766 - 0 KF, RR	21,000.00	.00	.00	-	-	-	-	-
SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES										
Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount \$				
1	3	CO	Contractual Obligations	50	These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present. Start: 01/01/1995 Last Modified: 07/01/2017	21,000.00				
Claim 1 of 1				Page 1 of 1						

Change Healthcare ERA Check 1 of 1		EFT/Check #: 09181130049	EFT/Check Date: 04/23/2018	EFT/Check Amount: \$.00	Payment Type: NON					
		Payer Name CGS - DME MAC JURISDICTION B		CH Payer Id: MR031	CH Process Date: 04/24/2018					
		Provider Name: NOVOCURE INC	Tax Id: 205063536	NPI 1255617569	Other Payee Id:					
		Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999		Addl. Payee Id 1255617569	Total PLB Adj Amt 21000					
Service Dates: 04/16/2018		Processing Status: 4 - Denied								
Payer Claim # / Medicare ICN #: 18107803853000		CH Claim Trace Id: 106238980798659	Place Of Service:	Total Adjustment Amount: \$.00						
Charge: \$ 21,000.00		Paid: \$ 00	Patient Responsibility: \$ -	Deductible: \$ -						
Co-Insurance: \$ -		Co-Pay: \$ -	Other/Crossover Insurance:							
Remark Codes:	N793	Alert: CMS is changing from the Medicare Health Insurance Claim number (HICN) to the new Medicare Beneficiary Identifier (MBI). You can use either the HICN or MBI during the transition period. Visit www.cms.gov/newcard for important dates and information about this change. Start: 07/01/2017 Last Modified: 11/01/2017 Notes: (Modified 11/1/2017)								
	MA13	Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07)								
	MA01	Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07)								
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PATIENT - SUBSCRIBER INFORMATION										
Patient Name: PROSSER, ANNIKEN S		Patient Id: 389044857A		Patient Control Number: 0001012479						
Corrected Patient/Subscriber Name:										
Subscriber Name:		Subscriber Id:		Group/Policy Id:						
Other Subscr. Name:		Other Subscriber Id:		Group/Policy Id:						
REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL										
Svc Line #	Service Date	Proc Code - Units Modifiers	Charge \$	Allowed \$	Not Allowed \$	Deductible \$	Co-Ins \$	Co-Pay \$	Late Filing Red \$	Paid \$
1	04/16/2018	E0766 - 0 KF, RR	21,000.00	.00	.00	-	-	-	-	-
SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES										
Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount \$				
1	3	CO	Contractual Obligations	50	These are non-covered services because this is not deemed a 'medical necessity' by the payer Usage: Refer	21,000.00				

4872

novocure

Invoice

Novocure Inc.
195 Commerce Way
Portsmouth, NH 03801

DATE: FEBRUARY 16, 2018
INVOICE # [103]

Bill To:
Anniken S. Prosser
W 2973 Farmstead Drive
Appleton, WI 54915

Ship To:
Anniken S. Prosser
W 2973 Farmstead Drive
Appleton, WI 54915

Ordered By: Jennifer Connelly, MD

ITEM #	DESCRIPTION	QTY	UNIT PRICE	LINE TOTAL
TFH9000	NOVO-TTF 100A PLUS TRANSDUCERS	1	\$21,000	\$21,000
SUBTOTAL				\$21,000
SALES TAX				0
TOTAL				\$21,000 Per Month

PLEASE REMIT TO: Novocure Inc., 195 Commerce Way, Portsmouth, NH 03801
Make all checks payable to Novocure Inc.

If you have any questions concerning this invoice, contact Justin Kelly, RN @ 603-501-4299.

4874

4875

Anniken S. Prosser
W2973 Farmstead Dr.
Appleton, WI 54915

October 24, 2017

Attn: Medicare Appeals
Re: Denial of My Cancer Treatment
Policy#: 389-04-4857-A

To whom it may concern:

This letter is in response to Medicare's denial of my physician's prior authorization request for coverage of Tumor Treatment Fields therapy (TTF) using Optune for my glioblastoma.

I am submitting this letter as an urgent member grievance so that I may obtain approval of my badly needed, FDA APPROVED, treatment for my cancer.

According to the letter we received from Medicare, the request for coverage for services was denied based upon the following reason: experimental.

First of all, I have to strongly disagree with this rationale. This treatment has been approved by the **United States Food and Drug Administration** for treatment of recurrent glioblastoma. Furthermore, my physician feels that this treatment is my best hope for slowing down the progression of my disease. I find it unconscionable that Medicare is second guessing the treatment decisions of my physician, Dr. Jennifer Connelly, who is one of the country's leading experts on this treatment.

TTF is my **best option** to treat this fatal disease. I have submitted the attached clinical information from my physicians as well as peer reviewed literature to assist you in considering approval of this treatment.

This procedure has been covered by many local and national insurance companies including: Medicare, Aetna (**Medical Policy Bulletin 0827**), Humana, Health Net (**Medical Policy Bulletin NMP523**), Health Partners (**Medical Policy Bulletin E003-01**), United Healthcare, Cigna (HMO and PPO), Anthem Blue Cross Blue Shield, BCBS Texas/Illinois/New Mexico/Oklahoma, Blue Cross Blue shield of Louisiana, Blue Cross Blue Shield of Michigan, HealthLink, Kaiser Permanente, Harvard Pilgrim Health Care, GHI, Horizon Blue Cross Blue Shield of New Jersey, NYS Empire Plan, Network Health Plan, and Blue Cross Blue Shield of Florida. This is only a representative sampling of payers covering Optune for this cancer indicating that there is enough "proven" evidence to warrant coverage for Optune in treating glioblastoma. **I am demanding that my clinical situation be reviewed by a board certified physician specializing in neuro-**

oncology or neurosurgery who has specific expertise in treating patients with glioblastoma with TTF.

I am a 34 year old woman with glioblastoma. I like drawing, writing lyrics and singing for the bands Antidote For Sorrow and Resisting the Solace. I also enjoy spending time with family and friends. I married Barry Prosser in September 2010. We have a son, Liam; he will be 4 years old on January 31st. I am currently not working. I enjoy vacations at the cottage.

I was diagnosed at the ER in February 2016. I had surgery at St. Elizabeth Hospital in Appleton Wisconsin and it was confirmed that I had GBM. I have had the following treatments; surgery, radiation, chemotherapy and Optune. I am off chemotherapy now, possibly may have to do more in the future still on Optune. I experienced the following symptoms; passing out, bad headaches, dizziness, throwing up, but these have been better with treatments and Optune. I have had fewer side effects with Optune and it is helping me so much. I am able to get up each day and be with my husband and son because of Optune. In my own words, I believe Optune is helping me very much; I am smiling because it's helping me keep the pain away!

After discussing treatment options with Dr. Jennifer Connelly, my doctor decided to prescribe Optune. Given the aggressive nature, and extremely limited treatment options of my disease, my doctor recommended I receive coverage for Optune, as it is the best FDA approved option at this time for treating my glioblastoma. I began utilizing TTFields on June 16, 2016.

Alternating electric field therapy (Optune) + adjuvant temozolomide is now an NCCN Category 2A recommendation following postoperative standard brain radiation therapy with concurrent temozolomide.

I am aware that my cancer is considered an "orphan disease," by the National Institutes of Health due to the rarity of people who get glioblastoma. Despite these interventions I have received to date, TTF therapy is my best hope to control my brain tumor.

I cannot emphasize enough the urgency and importance of this matter.

Should you have any additional questions regarding my condition or the proposed treatment, please feel free to contact me at (920)-257-3574.

I also give consent for Novocure to work on the appeal on my behalf.

Thank you for your timely consideration and hopeful approval of this case.

Sincerely, 

Anniken S. Prosser

Attachments



Optune® Prescription Form

Please fax or email signed and completed forms with medical records, face sheet, and copies of insurance card(s) to 603-501-4298 or support@novocure.com

I. PRESCRIPTION INFORMATION

Patient Name: <u>Anniken Prosser</u> <small>(required)</small>		Please check the appropriate box: <input type="checkbox"/> New Patient order <input checked="" type="checkbox"/> Renewal	
Date of Birth: <u>10/10/03</u> <small>(required)</small>			
Is this patient enrolling in an Investigator Sponsored Trial (IST) or Cooperative Group Trial (e.g. RTOG)? <input type="checkbox"/> Yes		If yes, which trial? _____	
Prescription Information			
Optune is comprised of: an Electric Field Generator (the "Device"), Transducer Arrays (the "Arrays"), power supply items, and accessories.			
ICD-10 Code: <u>C71.9</u> <small>(required)</small>		Diagnosis Description: <u>Glioblastoma Multiforme</u>	
I prescribe use of Optune, as described above, for a period of: <small>(check box required)</small>		<input type="checkbox"/> 3 months <input checked="" type="checkbox"/> 6 months	
Prescriber Information		Contact Information	
Prescriber Name (Last, First, Middle Initial): <u>Connolly Jennifer M</u> <small>(required)</small>		Name of Preferred Office Contact: <u>Carrie Guzlecki</u>	
NPI: <u>1780768531</u> <small>(required)</small>		Phone: <u>414-805-5231</u>	
Phone: <u>414-805-5204</u> Fax: <u>414-259-0469</u>		Email: <u>carrie.guzlecki@fredhst.com</u>	
By signing and dating, I attest that I am prescribing Optune (DO NOT SUBSTITUTE) as medically necessary. I have read and understand all safety information and other instructions for use included with Optune.			
Prescriber Signature: <u>[Signature]</u> <small>(required)</small>		Date: <u>04/13/2018</u> <small>(required)</small>	

II. ORDER INFORMATION

Treatment education, head preparation and array application will take place in the patient's home. Upon completion of the education session, the patient or caregiver may initiate treatment in the presence of Novocure personnel.

Preferred Treatment Start date (MM/DD/YYYY): _____

Please allow **5 business days** from submission of all required paperwork and preferred treatment start date.

Notes: <u>Continuation of treatment</u>
--



Optune® Prescription Form

Please fax or email signed and completed forms with medical records, face sheet, and copies of insurance card(s) to 603-501-4298 or support@novocure.com

I. PRESCRIPTION INFORMATION

Patient Information Patient Name: <u>Anniken Prosser</u> <small>(required)</small> Date of Birth: <u>10/10/83</u> <small>(required)</small> Is this patient enrolling in an Investigator Sponsored Trial (IST) or Cooperative Group Trial (e.g. RTOG)? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes, which trial? _____		Please check the appropriate box: <input type="checkbox"/> New Patient order <input checked="" type="checkbox"/> Renewal
Prescription Information Optune is comprised of: an Electric Field Generator (the "Device"), Transducer Arrays (the "Arrays"), power supply items, and accessories. ICD-10 Code: <u>C71.9</u> <small>(required)</small> Diagnosis Description: <u>Glioblastoma Multiforme</u> I prescribe use of Optune, as described above, for a period of: <small>(check box required)</small> <input type="checkbox"/> 3 months <input checked="" type="checkbox"/> 6 months		
Prescriber Information <u>Connelly Jennifer M</u> Prescriber Name (Last, First, Middle Initial): <small>(required)</small> NPI: <u>1780768531</u> <small>(required)</small> <u>414-805-5204</u> <u>414-259-0469</u> Phone Fax		Contact Information <u>Carrie Guzlecki</u> Name of Preferred Office Contact <u>414-805-5231</u> Phone <u>carrie.guzlecki@freedtext.com</u> Email
Prescriber Only to Complete. Original Signature Required. No Stamps. By signing and dating, I attest that I am prescribing Optune (DO NOT SUBSTITUTE) as medically necessary. I have read and understand all safety information and other instructions for use included with Optune. Prescriber Signature: <u>[Signature]</u> <small>(required)</small> Date (MM/DD/YYYY): <u>10/17/2017</u> <small>(required)</small>		

II. ORDER INFORMATION

Treatment education, head preparation and array application will take place in the patient's home. Upon completion of the education session, the patient or caregiver may initiate treatment in the presence of Novocure personnel.

Preferred Treatment Start date (MM/DD/YYYY): _____

Please allow **5 business days** from submission of all required paperwork and preferred treatment start date.

Notes Continuation



Optune™ Prescription Form

Fax the completed form with signature to 603-501-4298; or Email to support@novocure.com

III. PATIENT INFORMATION (PLEASE COMPLETE IN FULL)

Patient Information			
Permanent Address: <u>Wd 973 Farmstead Dr.</u>			
City: <u>Appleton</u>	State: <u>WI</u>	Zip: <u>54915</u>	Phone: <u>920-257-3574</u>
Family Contact: <u>Barry Prosser</u>		Phone: _____	
<input checked="" type="checkbox"/> Shipping and mailing address same as permanent address.		<input type="checkbox"/> Use the address below for shipping and mailing purposes related to equipment, supplies and billing. Patient must reside at this address:	
Shipping and Mailing Address: _____			
City: _____	State: _____	Zip: _____	Phone: _____
Insurance Information			
Primary Insurance: <u>National POS - Humana</u>			
Patient ID#: <u>100303812</u>	Insurance Phone Number: <u>866-427-7478</u>		
Group#: <u>668526</u>	Group Name: _____		
Primary Insured (Subscriber) Name: <u>Barry Prosser</u>			
Relationship to Patient: <u>Husband</u>	Subscriber Date of Birth: <u>5/24/85</u>		
**If you have secondary insurance, please attach this information if applicable.			

The use of "I" or "you" in this document refers to the patient named in the "Signatures" block.

Authorization to Release Records to Novocure

I authorize my physician and the practice, facility and hospital of my physician and any other holder of medical information about conditions for which I am being treated to release to Novocure Inc. and affiliated companies (together "Novocure") any information necessary for treatment, payment and healthcare operations related to my use of Optune. I authorize Novocure employees to deliver equipment and provide education in my home as well as attend my appointments as necessary to provide technical assistance to my physician and healthcare practitioners. I also authorize Novocure, my physician and the practice, facility and hospital of my physician and any other holder of medical information about conditions for which I am being treated to release such information to my insurer. These authorizations apply to my current physician and previous physicians. I understand that Novocure may and likely will use the information to seek a determination of whether my insurer will cover my use Optune.

Authorization To Discuss Care

I authorize Novocure to discuss my care with the family members and/or caregivers listed below. I may revoke this authorization at any time by calling or emailing Novocure at 857-281-9301 or support@novocure.com.

List all authorized individuals: Barry Prosser, Daniel Maas, Hilde Staven

Signatures: Anniken S. Prosser Barry Prosser Daniel Maas Hilde Staven

Patient Name (please print): Anniken S. Prosser Date: 5-31-16

If anyone other than patient completes or signs this form, please enter the following information:

Name: _____ Telephone Number: _____

Address: _____ City: _____

State: _____ Zip: _____

Relationship to Patient: _____ Reason for Signing: _____



Froedtert and the Medical College of Wisconsin Cancer Center
9200 W Wisconsin Ave
Milwaukee, WI 53226
414-805-6800

**REVIEW OF DENIED TREATMENT REQUEST
Life Threatening Condition**

June 14, 2016

Humana
Clinical Review Team
1100 Employers Boulevard
Green Bay, WI 54344

ATTN: Provider Appeal

RE: Anniken Prosser
Policy: 100303512
DOB: 10/10/1983

This letter is in response to the denial received after review of predetermination of benefits for my patient, Anniken Prosser. It is my understanding that Ms. Prosser is entitled to appeal this adverse benefit determination. Your denial letter indicates that you consider treatment with Optune to be investigational.

Please accept this letter as a formal appeal for coverage for Optune. I am also reiterating our request for a network exception for this patient due to the fact that there is no provider in the Humana network who can provide this service. I also request that a physician who is experienced in treating glioblastoma review this material as regulated by ERISA. **The type of physician familiar with the treatment of glioblastoma would be a neuro-oncologist or radiation oncologist with specific expertise treating GBM.**

Anniken Prosser is a young 32-year old female who initially presented with a severe migraine with associated nausea. MRI revealed a large enhancing left temporal cystic mass. She underwent a gross total resection on February 25, 2016. Pathology demonstrated glioblastoma multiforme. Following surgery, she went on to initiate treatment with radiation with concurrent Temodar. This was completed in May of 2016. After discussing treatment options with Ms. Prosser, I have decided to prescribe Optune in combination with temozolomide as this currently is the best option for treating her glioblastoma.

Optune is an innovative approach to cancer treatment, using tumor treating fields (TTFields) to interfere with the division of malignant cells. TTFields therapy is a locally or regionally delivered treatment that uses alternating electric fields to disrupt the rapid

Anniken S Prosser MR#: 10790724

cell division exhibited by cancer cells. GBM patients treated with TTFields wear insulated transducer arrays on the scalp attached to the portable electric field generator.

Optune received pre-market approval from the FDA for recurrent glioblastoma in April 2011. This approval was based on the results of a large randomized controlled trial of patients with recurrent GBM comparing Optune as a monotherapy to standard chemotherapy used in recurrent GBM. The results showed that treatment with Optune delivered comparable overall survival and progression free survival to chemotherapy with minimal toxicity and an improvement in patients quality of life compared to chemotherapy.

In 2015, Optune received pre market approval from the FDA for newly diagnosed glioblastoma in combination with temozolomide after standard surgical resection and radiation therapy. This approval was based on a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of newly diagnosed GBM patients treated with Optune and TMZ to those treated with TMZ alone. The results of the trial at the interim analysis showed superior efficacy both in progression free survival as well as overall survival. The data was so compelling that the independent data monitoring committee recommended the trial be terminated so that patients in the standard of care arm could cross over. The FDA approved the supplemental IDE to allow for crossover of patients on the control arm to the TTFields arm on December 1, 2014.

The pre-specified interim analysis of EF-14 trial data was conducted on the first 315 patients, representing approximately 50 percent of the targeted study population. The data show that:

Patients treated with TTFields together with temozolomide demonstrated a significant increase in progression free survival compared to temozolomide alone (median PFS of 7.1 months compared to 4.0 months, respectively, hazard ratio=0.63, p=0.001).

Patients treated with TTFields together with temozolomide demonstrated a significant increase in overall survival compared to temozolomide alone (median OS of 19.6 months compared to 16.6 months, respectively, hazard ratio=0.75, p=0.034).

The percentage of patients alive at 2 years in the TTFields together with temozolomide arm was 43% compared to 29% in the temozolomide alone arm.

Glioblastoma is an orphan disease, with limited available treatment options. Most payers are covering Optune for patients based on published medical policy as well as individual medical necessity review. Over 180 payers including Humana, have covered this therapy for members after an appeal process. This new data is an important advancement in the treatment of glioblastoma. It is imperative that Humana review their current policy for Optune and amend it to cover this therapy for patients with glioblastoma.

At Froedtert Health and Medical College of Wisconsin, Optune has been employed successfully for patients such as Ms. Prosser, and we have achieved excellent outcomes. We have been very fortunate in working with payers who specifically consider the above information as well as the patient's orphan disease status in issuing

Anniken S Prosser MR#: 10790724

positive coverage for our patients. I request Humana, offer the same consideration to Ms. Prosser, when considering this request for coverage of Optune.

It is my belief that Optune in combination with temozolomide is the most appropriate option for her at the present time. Based upon her orphan disease status, limited treatment options and the recently published peer reviewed data showing superiority of adding Optune to temozolomide I respectfully request reconsideration of the adverse benefit determination.

Sincerely,

James Buckley, MD

Jennifer Connelly, MD
Neurology
Neuro-Oncology - Board Certified
Froedtert Health and Medical College of Wisconsin
Phone: 414-805-5204
Fax: 414-805-5252

Anniken S Prosser MR#: 10790724

shaved (✓)

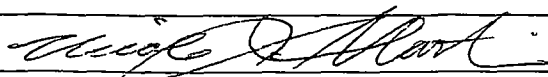
ASSESSMENT of NEED

Customer Name: MS. Anniken Prosser	Date: 6/8/16
Customer # 1012479	
DSS/Site Den Nancy Newberg / Fredrick + med. co.	Initiation: Home <input checked="" type="checkbox"/> Office <input type="checkbox"/>

Social Component: See Service Agreement	
Responsible Party/ Emergency Contact: Mr. Barry Prosser	Tel: 920-257-9525 * 920-257-3574

Economic Component: See Patient Document Acknowledgement
Patient acknowledges that financial responsibility has been discussed and agreed to: (Indicate date of welcome call and person spoken to) Pati 6/7/16

Environmental Component: NOT APPLICABLE - No Home Visits /Treatment initiated at HCP site			
Functional Component: (circle one)			
How did you hear about Optune Therapy? Physician			
What factors led to the decision to start treatment? Physician			
Did you receive a package from us containing printed material and DVD? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not Sure <input type="checkbox"/>			
Does patient live alone? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>		Patient has access to telephone: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Is patient residence? Home <input checked="" type="checkbox"/> Assisted Living <input type="checkbox"/> Other facility: <input type="checkbox"/>			
In what type of structure do you reside? House <input checked="" type="checkbox"/> - Apart/Condo- Assisting Living - Rehab Facility <input type="checkbox"/>			
Where will parking be? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Driveway			
How will we enter / exit residence? Front door, ring doorbell, 2 steps			
Should I be made aware of any safety concerns? ex lack of lighting, no elevator (if apt is not on 1 st floor) Please specify: N/A <input checked="" type="checkbox"/>			
Are there any pets in your home? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>		Cats #	Dogs # 2
Can pets be placed in another room while DSS present? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>		Other types #	
Is there smoking in the home? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>			
Is there anything that our DSS should know about the home environment or the people residing there that could be important for the safety of the visit? N/A <input checked="" type="checkbox"/>			
Is patient able to speak: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> If yes, what is his/her primary language? English			
Does patient have adequate electrical capacity to utilize device and recharge batteries? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>			
Does he/she require assistance with mobility? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>			
Are you employed? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> If so do you plan on continuing to work? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>			
If you are planning on continuing to work what is your occupation? N/A			
Have you discussed treatment during work hours with your employer? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>			

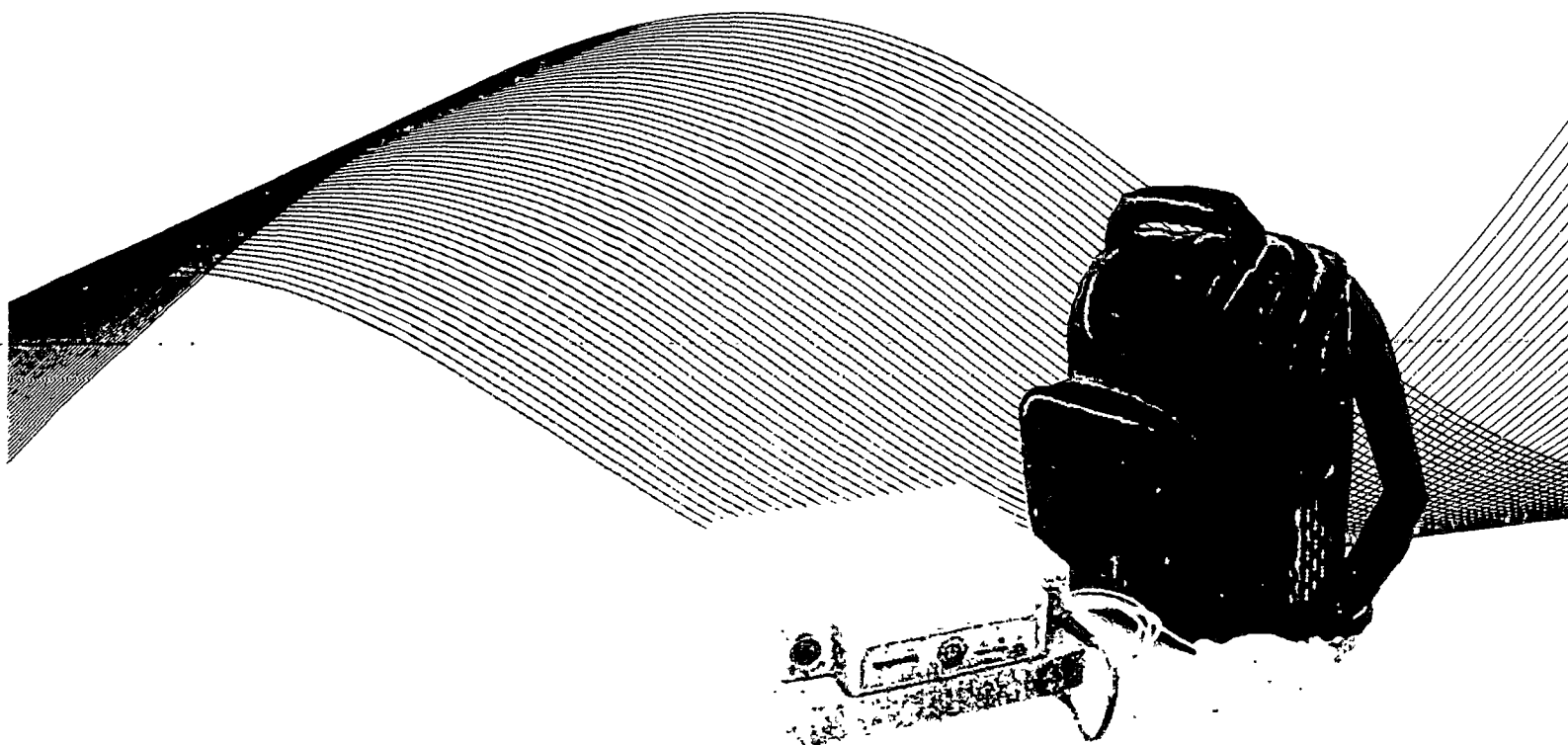
Type of verification that client/caregiver understands safe operation of equipment:	
See Technical Review Checklist: Yes - No	
Other: (Explain)	
Explain any special needs or additional training required (if applicable) N/A <input type="checkbox"/>	
Training on the Optune device is performed, conducted, and observed by certified physicians in accordance with FDA approval guidelines.	
Completed by: 	Date: 6/8/16

ANNIKEN PROSSER #1012479

NovoTTF™-100A System is now



OPTUNE™
SERVICE AGREEMENT



Supply Terms For Optune™

Background

Novocure™ inc. is referred to as "we" or "Novocure" in this service agreement ("Service Agreement"). The use of "you" or "your" refers to the patient named in the associated Service Agreement. All capitalized terms not defined herein have the meaning defined in the Service Agreement.

Supply Terms

Optune (the "System") is comprised of two main components (1) an Electric Field Generator (the "Device"); and (2) INE Transducer Arrays (the "Arrays") that are disposable supplies to the Device. The System also consists of power supply items and accessories.

Novocure's affiliates hold patents that cover the System, various components of the System, and using the System. Novocure hereby grants an expressly conditional license to you to use the inventions covered by those patents under the terms set forth herein. No other licenses to you is implied.

As an element of consideration for the grant of a license to you, you agree to pay Novocure a monthly fee for access to the System. Notwithstanding anything to the contrary contained in this agreement, any use of the System for which this element of consideration is absent is not licensed under the patents.

You acknowledge that, taken together, the consideration due to Novocure for access to the System reflects only the value of the "use" rights conferred by Novocure, and does not provide you with the same suite of rights that would accompany an unconditional sale. Notwithstanding anything to the contrary contained in this agreement, (1) you are not

licensed to use the Device with Arrays that were not purchased from Novocure, and (2) you are not licensed to use any given Array for more than seven (7) days.

You understand that the Device shall at all times remain the property of Novocure.

You understand and agree that Novocure has the right to inspect the System upon request and that you may be responsible for the replacement value of the System in the event it is lost, damaged, or stolen while in your possession or control.

You understand that (i) Novocure has the option to provide new or used equipment including the Device, power supplies and accessories, (ii) you shall not modify or alter any equipment provided to you by Novocure, (iii) you will notify Novocure immediately of any equipment problems, and (iv) the equipment is only to be used upon the order and direction of your doctor.

You understand that the System fees will continue until the date that you call Novocure to pick up the System. You understand that Novocure may stop providing the technical support for the System and may stop providing additional Arrays or replacement items if you fail to comply with the terms of the Service Agreement and Supply Terms, including failure to pay amounts owed or to remit payments due to Novocure that you receive directly from payers.

Patient Care Responsibilities

You understand and acknowledge that (1) your care is under the supervision and control of your treating physician or other healthcare provider (e.g., nurse practitioner, physician's assistant) who is appropriately licensed, trained and authorized to prescribe and administer the System, (2) your physician or other healthcare provider has prescribed the System as part of your treatment and has explained to you its risks, advantages, possible complications and

alternatives, and why it is considered necessary treatment for your condition, (3) Novocure's services do not include diagnostic, prescriptive or other functions pertaining to licensed physicians or healthcare providers, and (4) your physician or other healthcare provider is solely responsible for diagnosing and prescribing drugs, equipment and therapy for your condition and otherwise supervising and controlling your medical condition.

Financial Responsibilities

The rental fee for the System, including use of the Device, related power supplies/accessories and Arrays for 30 days is \$21,000.

Please call (855) 281-9301 if you have any questions about your financial responsibilities.

Novocure will review your insurance or third party payer (together "Payer") coverage for the purposes of providing you with an estimate of your out of pocket costs associated with the rental fee to use the Device and the purchase of Arrays. Novocure will also prequalify you for eligibility for our Patient Assistance Programs. Formal qualification for financial assistance will require a separate application and documentation of income.

Novocure will submit a claim to your Payer for the System and may appeal such claim if denied. Novocure will bill you for your financial responsibilities related to the System when i) your Payer affirms coverage for your use of the System at the list rental fees and supply prices for the System or ii) Novocure elects not to continue appeals of your case.

If your cost share for the System is not affordable or your Payer refuses to provide coverage for the System, you can also apply to Novocure for financial assistance

Please contact 855-281-9301 or email **support@novocure.com** to inquire about financial assistance programs.

Warranty Information

Novocure will provide a replacement Device in the event of malfunction that cannot be corrected over the phone by our technical support staff. Novocure will provide replacement Arrays in the event that the Transducer Arrays are defective to manufacturer standards. Novocure will provide replacement power supplies and accessories in accordance with the expected useful lifetime of these items. The above warranty is only valid if the System is used in accordance with the User Manual provided to you. This warranty is personal to you and non-transferable.

Lost equipment, including the Device, Arrays, power supplies and related accessories, and equipment damaged by you or your caregivers is not covered by this warranty.

Patient Information Form For Optune™

Background

Novocure™ Inc. is referred to as "Novocure" in this service agreement ("Service Agreement"). The use of "you" or "your" refers to the patient named in the associated Service Agreement. All capitalized terms not defined herein have the meaning defined in the Service Agreement.

Notice of Privacy Practices

THIS NOTICE DESCRIBES HOW HEALTH INFORMATION ABOUT YOU MAY BE USED AND DISCLOSED AND HOW YOU CAN GET ACCESS TO THIS INFORMATION. PLEASE REVIEW IT CAREFULLY.

Please contact 855-281-9301 or support@novocure.com if you have questions.

Purpose of this Notice

This notice will tell you about the ways in which Novocure may use and disclose your health information that identifies you ("PHI"). We also describe your rights and certain obligations we have regarding the use and disclosure of PHI.

Our Pledge Regarding Protected Health Information

We understand that health information about you and your health is personal. We are committed to protecting health information about you. We create a record of the products and services that we provide to you. We need this record to provide you with quality products and services used in your care and to comply with certain legal requirements. This notice applies to all of the PHI we use and disclose related to the products and services used in your care. Your personal doctor, healthcare provider and other entities

providing products or services to you may have different policies or notices regarding their use and disclosure of your PHI.

Our Legal Requirements

We are required by law to

- Make sure that health information that identifies you is kept private,
- Give you this notice of our legal duties and privacy practices with respect to PHI about you,
- Notify you if we are unable to agree to a requested restriction on how your information is used and disclosed,
- Accommodate reasonable requests that you may make to communicate PHI by alternative means or at alternative locations;
- Obtain your written authorization for purposes other than those listed below and permitted under law, and
- Follow the terms of the notice that currently is in effect.

Who Will Follow Our Privacy Practices

This notice describes Novocure's practices and that of all Novocure employees, staff and other company personnel for US operations only.

These entities, sites and locations follow the terms of this notice. Additionally, these entities sites and location may share PHI with each for treatment, payment or health care operations purpose described in this notice.

Your Rights Regarding Protected Health Information About You

You have the following rights regarding PHI we maintain about you:

Right to Inspect and Copy

You have the right to inspect and copy PHI that may be used to make decisions about your care. Usually this includes medical and billing records. To inspect and copy PHI that may be used to make decisions about you, please contact 855-281-9301 or support@novocure.com. We may charge a fee for copying requested files. We may deny your request to inspect and copy in certain circumstances. If you are denied access to PHI, you may request that the denial be reviewed. Another person chosen by us will review your request and the denial. We will comply with the outcome of that review.

Right to Amend

If you feel that PHI we have about you is incorrect or incomplete, you may ask us to amend the information. You have the right to request an amendment for as long as the information is kept by us. To request an amendment, please contact 855-281-9301 or support@novocure.com. You must provide a reason that supports your request. We may deny your request for an amendment if it does not include a reason to support that request. Additionally, we may deny your request if you ask us to amend information that

- Was not created by us, unless the person or entity that created the information is no longer available to make the amendment,
- Is not part of the PHI kept by or for us
- Is not part of the information which you would be permitted to inspect and copy; or
- Is accurate and complete

Right to Accounting of Disclosures

You have the right to request an "accounting of disclosures". This accounting is a list of the disclosure we made of PHI about you. Novocure will provide an accounting of all but the following types of disclosure:

- Those made for treatment, payment and health care operations;
- Those made to you about your own PHI;
- Those made to persons involved in your care or other notification purposes;
- Those made pursuant to an authorization signed by you disclosing specific uses and disclosures,
- Where the disclosures are part of a Limited Data Set (as defined in the Health Insurance Portability and Accountability Act);
- Where the disclosures are incidental to an otherwise permissible disclosure,
- For national security or intelligence purposes, and
- To correctional institutions or law enforcement custodial situations.

To request this list or accounting of disclosures, please contact 855-281-9301 or support@novocure.com. We may request that you submit the request in writing. Your request must state a time period that may not be longer than six years from the date of service. Your request should indicate in what form you want the list (i.e., paper or electronic). The first list you request within a 12-month period will be free. For additional lists, we will charge you for the costs of providing the lists. We will notify you of the cost involved and you may choose to withdraw or modify your request at the time before any costs are incurred.

Right to Request Restrictions

You have the right to request a restriction or limitation on the PHI we use or disclose about you for treatment, payment, or health care operations. You also have the right to request a limit on the PHI we disclose about you to someone who is involved in your care or the payment for your care, like a family member or friend. You may restrict disclosures of PHI to a health plan if you have paid out-of-pocket in full for the health care item or service. We are not required to agree to your request. If we do agree, we will comply with your request unless the information is needed to provide you emergency treatment. Please contact 855-281-9301 or support@novocure.com to request restrictions. We may request a written request. You must tell us i) what information you want to limit, ii) whether you want to limit our use, disclosure or both, and iii) to whom you want the limits to apply, for example, disclosures to your spouse.

Right to Request Confidential Communications

You have the right to request that we communicate with you about medical matters in a certain way or at a certain location. For example, you can ask that we only contact you at work or by mail. Please contact 855-281-9301 or support@novocure.com to request confidential communications. We may request a written request. We will accommodate all reasonable requests. Your request must specify how or where you wish to be contacted.

Right to Revoke Authorization

You have the right, in those instances where written authorization is required, to revoke such authorization to use or disclose PHI except to the extent action has already been taken. Such revocation must be in writing.

Right to a Paper Copy of this Notice

You have the right to a paper copy of this notice. You may ask us to give you a copy of this notice at any time. Even if you have agreed to receive this notice electronically, you are still entitled to a paper copy of this notice. Please contact 855-281-9301 or support@novocure.com to request a paper copy.

How We May Use and Disclose Protected Health Information About You

The following categories describe different ways that we are permitted to use and disclose PHI as a health care provider. Certain of these categories may not apply to our business and we may not actually use or disclose your PHI for such purposes. Not every use or disclosure in a category will be listed. However, all of the ways we are permitted or required to use and disclose PHI, without your authorization, will fall within one of the categories.

For Treatment

We may use or disclosure PHI about you to assist healthcare professionals and providers provide you with medical treatment or services. For example, we may provide PHI related to your use of our products or services to your physician and the staff at your physician's practice to assist your physician in maintaining appropriate use of the device.

For Payment

We may use and disclose PHI about you so that the products and services we provide you may be billed to and payment may be collected from you, an insurance company or a third party. For example, we may need to receive from or disclose to your health plan, Medicare, or the medical facility you resided in information about the products and services we provided to you so they or another responsible payor can pay us. This may specifically include information required for the Prescription Order Form, Assignment of Benefits,

MRIs, and medical record information. We may also tell your health care provider or plan about a product or service you are going to receive to obtain prior approval or to determine whether your provider or plan will cover that product or service.

For Health Care Operations

We may use and disclose PHI about you for our health care operations and we may use and disclose PHI about you to other health care providers involved in your care for certain health care operations they have to undertake. These uses and disclosures are necessary to run our company and make sure that users of our products receive the most cost effective and therapeutic products possible. Examples of health care operations activities by Novocure include but are not limited to delivery, pick-up and service functions, collection efforts, internal auditing, business planning (including analysis of product length of use, utility, or development/improvement of reimbursement methods or policy), assessing the quality of care and outcomes in your case and similar cases, and quality assurance/improvement activities. We may also combine PHI about many patients to decide what additional products and services we should offer, what products and services are not needed, and to justify how effective our products are in the care of individuals such as you. We may also disclose information to medical facilities and independent researchers for review and learning purposes. We may remove information that identifies you from this set of PHI so others may use it to study health care and health care delivery without learning who the specific patients are.

Notice/Reminders

We may use and disclose PHI to contact you or arrange for your health care provider to contact you regarding product delivery, maintenance, in-service or pick-up.

Individuals Involved in Your Care or Payment for Your Care

We may disclose to a family member, other relative, close personal friend of yours or any other person identified by you PHI directly relevant to such person's involvement with your care or payment for your health care when you are present for, or otherwise available prior to, a disclosure and you are able to make health care decisions, if: (i) we obtain your agreement, (ii) we provide you with the opportunity to object to the disclosure and you failed to do so; or (iii) we infer from the circumstances, based upon professional judgment, that you do not object to the disclosure. We may obtain your oral agreement or disagreement to a disclosure. However, if you are not present, or the opportunity to agree or object to the disclosure cannot practicably be provided because of your incapacity or an emergency circumstance, we may, in the exercise of professional judgment, determine whether the disclosure is in your best interests, and, if so, disclose only PHI that is directly relevant to the person's involvement with your health care.

Research

Under certain circumstances, we may use and disclose PHI about you for research purposes. For example, a research project may involve comparing the health and recovery of all patients who received on product or service for the same condition. We may also disclose PHI about you to people preparing to conduct a research project, for example to help them look for patients with specific medical circumstances. We will in most circumstances ask for your specific authorization if the researcher will have access to your name, address or other identifying information that reveals who you are.

As Required by Law

We will disclose PHI about you when required to do so by federal, state or local law. For example, we may disclose information for judicial and administrative proceedings pursuant to legal authority, to report information related to victims of abuse, neglect or domestic violence, or to assist law enforcement officials in their law enforcement duties.

Government Functions

We may use and disclose PHI about you as required for specialized government functions such as protection of public officials, reporting to various branches of the armed services or national security activities authorized by law.

To Avert a Serious Threat to Health or Safety

We may use and disclose PHI about you when necessary to prevent a serious threat to your health and safety or the health and safety of the public or another person. Any disclosure, however, would only be to someone able to help prevent the threat.

Business Transfers

There may arise in the course of business the acquisition or sale of our business assets (Business Transfers). Such Business Transfers may involve the sale or purchase of PHI. Also, in the event that Novocure Inc. or its parent entity, Novocure™ Limited of Jersey (Channel Islands), or any subsidiary of Novocure Limited are acquired or substantially all of its assets are acquired, PHI likely will be one of the transferred assets.

Workers' Compensation

We may release PHI about you for workers' compensation or similar programs. These programs provide benefits for work-related injuries or illness.

Public Health Activities

We may use or disclose your PHI to a health oversight agency for activities authorized by law. These oversight activities include, for example, audits, investigations, inspections, and licensure. These activities are necessary for the government to monitor the health care system, government programs, and compliance with civil rights laws.

Lawsuits and Disputes

If you are involved in a lawsuit or a dispute, we may disclose PHI about you in response to a court or administrative order. We may also disclose PHI about you in response to a subpoena, discovery request, or other lawful process by someone else involved in the dispute, but only if efforts have been made to tell you about the request and obtain your written authorization or to obtain an order protecting the information requested.

Other Uses of Protected Health Information

Other uses and disclosures of PHI not covered by this notice or otherwise permitted by laws that apply to us will be made only with your written authorization. Your authorization will not be required if Novocure uses or discloses health information for purposes other than as covered by this notice or permitted by law if Novocure removes any information that individually identifies you before disclosing the remaining information. If you provide us authorization to use or disclose PHI about you, you may revoke that permission, in writing, at any time. If you revoke your permission we will no longer use or disclose PHI about you for the reasons covered by your written authorization. You understand that we are unable to take back any disclosures we have already made with your permission, and that we are required to retain our records of the products and services that we provided to you.

Changes to This Notice

We reserve the right to change our information practices and to make the new provisions effective for all PHI we maintain. We also reserve the right to change this notice at any time. We reserve the right to make the revised or changed notice effective for PHI we already have about you as well as any information we receive in the future. You may request current version of our privacy practices by contacting 855-281-9301 or support@novocure.com

Complaints

If you believe your privacy rights have been violated, you may file a complaint with us or with the Secretary of the Department of Health and Human Services. To file a complaint with us, you must submit it in writing to Novocure. Please contact 855-281-9301 or support@novocure.com to request the current mailing instructions for Novocure.

Patient Bill of Rights

Your Rights

As a patient you have certain rights including but not limited to the following:

- **Information.** Patients have the right to receive accurate, easily understood information to assist them in making informed choices.
- **Choice.** Patients have the right to a choice of health care providers.
- **Access to Emergency Services.** Patients have the right to access emergency health services when and where the need arises
- **Being a Full Partner in Health Care Decisions.** Patients have the right to participate fully in all decisions related to their health care.
- **Care Without Discrimination.** Patients have the right to considerate, respectful care from all members of the healthcare industry at all times and under all circumstances.
- **Privacy.** Patients have the right to communication with healthcare providers in confidence and to have the confidentiality of their individual identifiable health care information protected.
- **Speedy Complaint Resolution.** Patients have the right to a fair and efficient process for resolving differences.

Your Responsibilities

As a patient you have certain responsibilities including, but not limited to the following

- **Provide information.** You must give accurate and complete health information concerning your past illnesses, hospital stays, medications, allergies and other pertinent items. You are also responsible for providing documentation required by your insurance company
- **Ask questions.** You must ask question when you do not understand medical conditions, equipment, instructions, and or medical terminology.
- **Follow instructions.** You must adhere to your developed and updated treatment plans.
- **Accept consequences** You must accept consequences for not following the treatment plan instructions of your doctor and nurse.
- **Understand your benefits.** You must understand what your insurance company will or will not authorize for durable medical equipment (DME) benefits.
- **Product responsibilities.** Your doctor has prescribed this medical device for the treatment and care of your disease. This is a rental device and cannot be resold. Prompt return of this device is required once therapy is completed.

- **Show respect and consideration.** You must show respect and consideration to those who are assisting you in your treatment plan including Novocure's staff providing technical support for your use of the device.
- **Meet financial commitments.** You are responsible for any applicable co-insurance, co-payments, or private pay amounts not covered by your insurance provider.

Contact Information for Questions or Complaints

Any questions, concerns or complaints may be addressed to 855-281-9301 (toll-free) or support@novocure.com.

You may contact the Accreditation Commission on Health Care to report any concerns or register a complaint by calling ACHC toll-free at 855-937-2242 or 919-785-1214 and request the Complaints Department.

Authorization to Release Information; Assignment of Benefits; Acknowledgment of Education and Training; Acknowledgment of Receipt of Certain Forms; and Delivery Confirmation

Background

Optune™ (the "System") is comprised of two main components: (1) an Electric Field Generator (the "Device"); and (2) INE Transducer Arrays (the "Arrays") that are disposable supplies to the Device. Novocure™ Inc. is referred to as "we" or "Novocure" in this service agreement ("Service Agreement"). The use of "you" in this Service Agreement refers to the patient named in this Service Agreement.

Authorization to Release Information

You authorize your physician and the practice, facility and hospital of your physician and any other holder of medical information about conditions for which you are being treated to release to Novocure any information necessary for treatment, payment and healthcare operations related to your use of the System. You also authorize Novocure, your physician and the practice, facility and hospital of your physician and any other holder of medical information about conditions for which you are being treated to release such information to your insurance company and any other entity paying for your medical care ("your payer"). These authorizations apply to your current physician and previous physicians, their practices, facilities and hospitals.

Authorization To Discuss Care

You authorize Novocure to discuss your care with the family members and/or caregivers listed below. You may revoke this authorization at any time by calling or emailing Novocure at 855-281-9301 or support@novocure.com.

List all authorized individuals

Barry Prosser, Daniel Mees

Assignment of Benefits

You give Novocure the right to bill for and receive payments for your medical care and you direct your payer to pay Novocure directly for the System. You agree to forward all payments to Novocure in the event that your payer pays you directly, and you acknowledge that Novocure may stop supplying the

System to you if you fail to do so. You acknowledge receipt of the supply terms and information on financial responsibilities and warranties ("Supply Terms") from Novocure and agree to those terms

Acknowledgment of Education and Training

You have received education on the use and maintenance of the System. You have been provided a technical support phone number for questions about use of the System. You have been provided with the User Manual for the System. You consent to accept phone calls from Novocure for technical support and health care operations matters, including billing matters.

Acknowledgment of Certain Forms

You acknowledge that you have received, read and accepted all terms and conditions set forth in these documents.

1. **Patient Information Form**, which includes a Statement of Privacy Practices, Patient Bill of Rights, and Contact Information for Novocure for Questions and/or Complaints

We are required by regulation to respond to your complaints within 5 calendar days and respond back to you with the results of our investigation within 14 calendar days

2. **Supply Terms**, which includes Financial Responsibilities and Warranty information

3. **Advanced Beneficiary Notice**
(for Medicare patients only)

The products and/or services provided to you by Novocure are subject to the supplier standards contained in the Federal regulations shown at 42 Code of Federal Regulations Section 424.57©. These standards concern business professional and operational matters (e.g., honoring warranties and hours of operation). The full text of these standards can be obtained at <http://ecfr.gpoaccess.gov>. Upon request we will furnish you a written copy of the standards.

Please sign here:

Barry Prosser
Signature

6-16-16
Date

Delivery Confirmation

You acknowledge receipt of the equipment and supplies listed below

Part Description	Quantity	S/N or Lot Number
Optune™ Device E0766	1	TFM00801
Connection Cable	2	CAD13343 CAD14244
Portable Charger	1	ICH10698
Power Supply	1	SPS11414
Rack	1	PBL11834
Portable Battery	4	IBH17598 IBH11571 IBH14486 IBH14609
Black Transducer Array (Lot#) E0766	20	C601203
White Transducer Array (Lot#) E0766	20	C1604101
Device Combo Bag	1	
Power Cord	2	
Manual – Instructions for Use	1	
Operation Manual	1	
Self-Exchange Kit	1	

You agree to the terms of this Service Agreement and of the related forms that you have received.
The authorizations granted in this Service Agreement will expire two (2) years from the date signed below.

Signatures

Patient Name (please print): Anniken Prosser
Patient or authorized signature: Anniken Prosser Date 6-16-16

If anyone other than patient completes or signs this form, please enter the following information:

Name _____ Telephone Number _____
Address _____
City, State, Zip _____
Relationship to Patient _____
Reason for Signing: _____

For Novocure™ Use Only

Delivery Person/Service Print Nancy Newberg
Signature/Tracking# Nancy Newberg
Delivery Date 6/16/16
Novocure Patient ID# 1012479
Novocure Order # 18251

novocure™

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QSF-DME-002140 10 May 2016, 07:28:05 am, Printed by: BMILLS



PATIENT INFORMATION AND CONSENT

Optune™ Treatment Education Visit

IMPORTANT: Please do not sign this consent until you read and understand the consent. Please discuss any questions you may have with the Novocure™ personnel that will conduct your treatment education. You should feel that signing this form is something you are doing voluntarily. If you feel that you are under pressure, please do not sign this form. Please read this consent to understand the purpose and nature of this treatment education visit. If you sign this consent, you confirm that you understand the purpose and nature of this visit and that you give your consent to participate in the treatment education.

You or your physician has requested that Novocure personnel conduct a treatment education visit for Optune. ***If you want to hold this session at your physician's office, please tell Novocure personnel prior to the start of the session and do not sign this consent.***

You (and your caregiver(s)) are being trained regarding the use of Optune. As part of this session, you will be taught about the following:

- Use of Optune, including how to change the battery, how to recharge the battery and connect to an external power supply, how to connect the transducer arrays connectors to the connector box, and what to do when an alarm occurs;
- How to shave your head to maintain appropriate transducer array contact with your scalp
- How to apply the transducer arrays to your scalp, and
- How to turn Optune "on" and "off"

By signing this consent, you confirm your understanding that

- Novocure personnel conducting your treatment education session are not physicians or healthcare providers. Please talk to your

physician regarding your medical care and any questions you may have regarding your medical condition and your treatment options.

- Novocure personnel are providing education regarding the use of Optune. You will also receive the Patient Instruction and Operation Manual (PIOM) for Optune, which will be a resource for any questions you may have after this session.
- Novocure personnel will teach you and/or your caregiver(s) how to shave your head and apply the transducer arrays. You and/or your caregiver(s) will shave your head and apply the transducer arrays, with assistance from Novocure personnel. Novocure personnel may touch you during the session while teaching you and/or your caregiver(s) to perform these activities.

– You may suffer cuts and possible skin irritation associated with shaving your head.

– You may suffer mild to moderate skin irritation associated with application of the transducer arrays.

– You should contact your physician regarding care for any injury you suffer during this treatment education session.

- Novocure personnel will show you and/or your caregiver(s) how to begin therapy by turning Optune "on." It is your decision when to begin Optune therapy. If you initiate therapy today, please initiate therapy in the presence of Novocure personnel, who will confirm Optune is working appropriately.
- If you have a medical issue during the session, you consent to Novocure personnel calling 911 and/or emergency medical services.
- Your physician will confirm that you understand how to use Optune and its use at your next physician visit.

I agree to participate in the treatment/education session described and to allow Novocure personnel to conduct the session.

By signing this form, I have not given up any of my legal rights.

Please print your name Anniken Prosser

6-16-16 Anniken Prosser

(Date) (Signature of Participant)

Technical Review of Optune™

Patient Name: <u>Anniken Prosser</u>	Patient #: <u>1012479</u>
Patient Signature: <u>Anniken Prosser</u>	Date: <u>6-16-16</u>

Optune <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Overview and Description • Powering On/Off

Connection Cable <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Overview and Description • Connecting to Device

Powering the Device <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Portable Batteries • Connecting Power Sources • Charging Portable Batteries • Battery Rack and Charger • Wall Power Supply

Carrier Bag <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Placement and Carry Options

Transducer Arrays <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Overview and Description • Transducer Array Components • Placement Recommendations • How to Shift Paired Arrays at Each Array Change • Skin Observation and Care • Showering • Disposal and Reorder

Troubleshooting <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Alarms • Common Causes • Correcting Alarms • Novocure Support Information • Equipment Exchange Process

Placing the Arrays <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Preparing the Head • Review NovoTAL-Map • Applying the Transducer Arrays

Patient Literature <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • PIOM • Patient Quick Start Guide

Novocure Employee Name: <u>Nancy Newberg</u>	Date: <u>6/16/16</u>
Novocure Employee Signature: <u>Nancy Newberg</u>	

novocure

TM-MA-002 Rev 06

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Printed on: 20 May 2016, 07:02:02 am; Printed by: BMILLS Expiration Date

PAGE 1 of 1

Prosser, Anniken S

MRN: 10790724

Progress Notes Encounter Date: 9/19/2018**Connelly, Jennifer M, MD**

Neurology

Neuro-Oncology followup Visit

RE: Anniken S Prosser

MR#: 10790724

DOB: 10/10/1983

Date of Clinic Visit: 9/19/2018

Chief Complaint: GBM

History of Present Illness:

Ms. Prosser is a 34 Y/o lady who returns to the Neuro-Oncology clinic for further evaluation and management of a left temporal Grade 4 astrocytoma. She comes to clinic today with her husband and son, Liam. Since her last visit, she has remained on TTFields (compliance 87% in August). She is using clobetasol as needed. She denies any skin issues. She has headaches with her menses. She has otherwise been healthy.

Neuro-oncology History:

H/o migraines - started in mid-20's; possibly secondary to Crohn's meds; diffuse in nature and daily

Feb. 14, 2016 - intractable migraine

MRI - large left cystic temporal mass

Feb. 25, 2016 - left craniotomy - GBM

May 2016 - completed radiation with Dr. Editha Kruegar with concurrent temodar with Dr. Jasleen Randhawa

June 2016 - continue with adjuvant temodar

June 16, 2016 - started Optune TTFields

April 2017 - completed 12 cycles of temodar; continue TTFields

Past Medical History:

Diagnosis	Date
• Crohn's disease (*)	
• GBM (glioblastoma multiforme) (*)	2/25/16
left temporal	
• WPW (Wolff-Parkinson-White syndrome) 1999	
s/p ablation	

Social History**Social History**

• Marital status:	Married
Spouse name:	N/A
• Number of children:	N/A
• Years of education:	N/A

Ears, Nose, Mouth, Throat - denies difficulty swallowing
 Cardiovascular - denies chest pain
 Respiratory - denies SOB, cough
 Gastrointestinal - denies constipation, diarrhea
 Genitourinary - denies dysuria
 Integumentary - as per HPI
 Neurological - as per HPI
 Psych - denies depression, anxiety

Exam:

Vitals:

09/19/18 1443
 BP: 114/76
 Pulse: 75
 Patient Position: Sitting
 During BP:
 BP taken on: Right Upper Arm
 Cuff Size: Adult Regular
 Resp: 16
 Temp: 97.1 °F (36.2 °C)
 SpO2: 100%
 Weight: 52 kg (114 lb 10.2 oz)

General: no distress.
 Skin: mild contact dermatitis

Neurologic:

Mental Status: Alert and attentive. Oriented to person, place, time and reason for visit. Language fluent with intact comprehension. Immediate recall, working memory, and long-term memory intact. No neglect.

Cranial Nerves:

- 1 - not assessed
- 2 - Fully intact visual fields bilaterally via confrontation.
- 3, 4, 6 - extraocular movements intact and conjugate. Normal smooth pursuit. Normal saccades.
- 5 - normal facial sensation to light touch bilaterally.
- 7 - symmetric facies with normal smile, palpebral fractures, nasal labial folds and forced eyelid closure.
- 8 - grossly intact
- 9, 10 - symmetric palate elevation.
- 11 - 5/5 head turning, bilaterally.
- 12 - tongue midline at rest and upon protrusion.

Motor: 5/5 throughout with normal bulk and tone; no evidence of pronation
 Finger tapping: normal frequency and amplitude bilaterally

Reflexes: 2+ throughout

Sensation: Intact to light touch in all 4 extremities

Motor Integration (Cerebellar):

Finger to Nose: Normal bilaterally without ataxia, dysmetria, or tremor.

Results

PACS Images

Show images for MR BRAIN WO + W CONT

MR BRAIN WO + W CONT [70553.000] (Accession#
FH1166-091918) (Order# 224683787)
MR RCBV SEQUENCE [76498.003] (Accession#
FH1165-091918) (Order# 224683788)

Study Result

Exam: MR BRAIN WO + W CONT [70553.000] **Service Date:**
9/19/18

Impression:

1. Left temporal treatment bed with small focus of enhancement at the posterior medial margin of the left anterior temporal resection cavity, similar to the prior study.
2. An area of nonenhancing abnormal long TR signal with gyral expansion in the left lateral and medial temporal lobes and in the left insular cortex, similar to the prior study. No new lesions.
3. No evidence for abnormal vascularity on MR perfusion study.

Narrative:

Examination:

1. MRI of the brain without and with contrast.
2. MR perfusion study with contrast.

Clinical information: 34-year-old female with left temporal GBM, status postop and post chemoradiation.

Comparison: 06/13/2018.

Technique: Multisequence, multiplanar MR imaging of the brain was performed without and with contrast. Postcontrast imaging was performed after the intravenous injection of 5 mL Gadavist. An additional 5 mL of Gadavist were administered for MR perfusion study.

Postoperative changes from prior left temporal craniotomy are again seen. An anterior left temporal resection cavity is seen, similar in size and appearance to the prior study. Linear enhancement at the posteromedial margin of the resection cavity is again seen, similar to the prior study. There is no definite nodular enhancement. Elsewhere along the resection cavity, no abnormal enhancement is seen.

Gyral expansion and nonenhancing abnormal long TR signal involving the left lateral and medial temporal lobes and the left insular cortex is again noted, similar in extent to the prior study. No new lesions are identified.

Minor scattered sinus mucosal disease is seen. Orbits and mastoids are unremarkable.

MR BRAIN WO + W CONT (Order #224683787) on 9/19/2018 - Order Result History Report

Image(s) reviewed and final report confirmed by MOHIT AGARWAL MD on Wed Sep 19, 2018 6:02:27 PM CDT

MOHIT AGARWAL, MD

Show images for MR BRAIN WO + W CONT

History, Radiology - Scan on 9/19/2018 1:10 PM by Larsen, Jennifer, RTR : mr history brain/rcbv

Open Hard Copy Result Report (Order #224683787 - MR BRAIN WO + W CONT)

Prosser, Annika S (MR # 10750724) Printed by Guzzieck, Carrie A, RN [27113] at 12/7/18 8:58 AM⁴⁹⁰⁶

Prosser, Anniken S

MRN: 10790724

Progress Notes Encounter Date: 6/13/2018**Connelly, Jennifer M, MD**

Neurology

Neuro-Oncology followup Visit

RE: Anniken S Prosser

MR#: 10790724

DOB: 10/10/1983

Date of Clinic Visit: 6/13/2018

Chief Complaint: GBM

History of Present Illness:

Ms. Prosser is a 34 Y/o lady who returns to the Neuro-Oncology clinic for further evaluation and management of a left temporal Grade 4 astrocytoma. She comes to clinic today with her husband and son, Liam. Since her last visit, she has remained on TTFields (compliance 87% in May). She is using clobetasol as needed. Her skin is doing well. They went on vacation to Florida last month and she was able to manage the heat and humidity and remained compliance with Optune. She denies any neuro symptoms. She inquires about the use of Optune should they decide to expand their family.

Neuro-oncology History:

H/o migraines - started in mid-20's; possibly secondary to Crohn's meds; diffuse in nature and daily

Feb. 14, 2016 - intractable migraine

MRI - large left cystic temporal mass

Feb. 25, 2016 - left craniotomy - GBM

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• GBM (glioblastoma multiforme) (*)	2/25/16
left temporal	
• WPW (Wolff-Parkinson-White syndrome) 1999	
s/p ablation	

Social History**Social History**

• Marital status:	Married
Spouse name:	N/A

- Number of children: N/A
- Years of education: N/A

Social History Main Topics

- Smoking status: Never Smoker
- Smokeless tobacco: Never Used
- Alcohol use: Not on file
- Drug use: Unknown
- Sexual activity: Not on file

Other Topics

- Not on file

Concern

Social History Narrative

- No narrative on file

Family History

Problem	Relation	Age of Onset
• Breast Cancer	Maternal Aunt	
• Ovarian Cancer onset in 20's	Maternal Cousin	
• Cancer onset in 80's - leukemia	Paternal Grandfather	

Current Outpatient Prescriptions

Medication	Sig
• acetaminophen (TYLENOL) 500 MG tablet	Take 500 mg by mouth every 4 hours as needed.
• Calcium Citrate-Vitamin D (CALCIUM + D PO)	Take 2 tablets by mouth daily.
• clobetasol propionate (CLOBEVATE OR TEMOVATE) 0.05 % cream	Apply as needed to scalp rash. Leave on for 20-60 minutes, cleanse lightly with alcohol and apply arrays.
• fish oil	Take 1 tablet by mouth daily.
• Multiple Vitamins-Minerals (WOMENS DAILY MULTIVITAMIN PO)	Take 1 tablet by mouth daily.
• NON FORMULARY MEDICATION	Reasonsreishi mushroom for immune support
• TURMERIC CURCUMIN PO	Take 1 tablet by mouth daily. Patient uses brand Curcubrain

Allergies

Allergen	Reactions
• Ragweed	EENT - watery eyes
• Sulfa Drugs	RESP - shortness of breath

ROS:

Constitutional - denies fevers, weight loss
 Eyes - denies diplopia
 Ears, Nose, Mouth, Throat - denies difficulty swallowing
 Cardiovascular - denies chest pain
 Respiratory - denies SOB, cough
 Gastrointestinal - denies constipation, diarrhea
 Genitourinary - denies dysuria
 Integumentary - as per HPI
 Neurological - as per HPI
 Psych - denies depression, anxiety

Exam:

Vitals:

06/13/18 1417
 BP: 132/83
 Pulse: 72
 Resp: 14
 Temp: 97.2 °F (36.2 °C)
 SpO2: 99%
 Weight: 51.3 kg (113 lb 1.5 oz)

General: no distress.

Skin: mild contact dermatitis

Neurologic:

Mental Status: Alert and attentive. Oriented to person, place, time and reason for visit. Language fluent with intact comprehension. Immediate recall, working memory, and long-term memory intact. No neglect.

Cranial Nerves:

1 - not assessed
 2 - Fully intact visual fields bilaterally via confrontation.
 3, 4, 6 - extraocular movements intact and conjugate. Normal smooth pursuit. Normal saccades.
 5 - normal facial sensation to light touch bilaterally.
 7 - symmetric facies with normal smile, palpebral fractures, nasal labial folds and forced eyelid closure.
 8 - grossly intact
 9, 10 - symmetric palate elevation.
 11 - 5/5 head turning, bilaterally.
 12 - tongue midline at rest and upon protrusion.

Motor: 5/5 throughout with normal bulk and tone; no evidence of pronation

Finger tapping: normal frequency and amplitude bilaterally

Reflexes: 2+ throughout

Sensation: Intact to light touch in all 4 extremities

Motor Integration (Cerebellar):

Finger to Nose: Normal bilaterally without ataxia, dysmetria, or tremor.

Rapid Alternating Movements: Normal with bilateral hands

Gait:

Results

PACS Images

Show images for MR BRAIN WO + W CONT

MR BRAIN WO + W CONT [70553.000] (Accession#
FH0149-061318) (Order# 216928898)
MR RCBV SEQUENCE [76498.003] (Accession#
FH0148-061318) (Order# 216928899)

Study Result

Exam: MR BRAIN WO + W CONT [70553.000] Service Date:
6/13/18

Impression:

No evidence of disease progression. Left temporal resection cavity with linear enhancement within the anterior and posteromedial aspects of the cavity as well as T2/FLAIR hyperintensity of the adjacent left temporal lobe, insula, and subinsular white matter appear unchanged from 03/15/2018.

Narrative:

Examination: MRI of the brain without and with contrast; MR perfusion of the brain with contrast.

Clinical information: 34-year-old female with glioblastoma multiforme status post resection 02/25/2016, radiation with concurrent temozolomide completed 5/2016, adjuvant temozolomide and OPTune 6/2016 completed 4/2017.

Comparison: 12/14/2017, 03/15/2018, 02/24/2016.

Technique: Multisequence, multiplanar MR imaging of the brain was performed without and with contrast. MR perfusion was also performed using dynamic susceptibility contrast (DSC) method with echoplanar technique after contrast administration. rCBV and rCBF data were post-processed off-line with the IB Neuro software package. The patient received a total of 15 mL Gadavist.

Findings:

Post surgical changes: Postoperative changes of large left frontal-squamous temporal-parietal craniotomy with

underlying resection cavity involving the anterolateral aspect of the left temporal lobe. There is a small amount of irregular enhancement along the posterior medial margin of the resection cavity that appears unchanged, may represent choroid plexus from the left temporal horn. Unchanged linear enhancement within the anterior aspect of the resection cavity. Thin susceptibility artifact along the margin of the resection cavity compatible with hemosiderin deposition from prior blood products. These findings appear unchanged from 03/15/2018.

White matter: There is confluent T2/FLAIR hyperintensity involving the white matter and cortex of the left temporal lobe medial and posterior to the resection cavity. This signal abnormality also extends through the temporal stem into the insula and subinsular white matter. This appears unchanged.

Additional comments: There are a few punctate foci of susceptibility artifact within the left supratentorial brain parenchyma compatible with hemosiderin deposition from chronic microhemorrhages. There is no midline shift, abnormal extra-axial fluid collection, or acute intracranial hemorrhage. The basal cisterns are patent.

Ventricles: There is no hydrocephalus.

Restricted diffusion: There is no restricted diffusion to suggest acute or subacute ischemic infarct.

Enhancement: No abnormal intra-axial or extra-axial enhancement is identified.

Midline structures: The pituitary and craniocervical junction are normal.

Flow voids: The normal major intracranial arterial flow voids are visualized.

Sinuses and mastoid air cells: The imaged paranasal sinuses and mastoid air cells are clear.

Orbits: The imaged orbits are unremarkable.

Marrow: T1 marrow signal of the skull and upper cervical spine is appropriate for age.

MR perfusion: Susceptibility artifact limits evaluation of perfusion signal at the treatment site. However, no focal hyperperfusion is identified to suggest tumor angiogenesis.

Result History

MR BRAIN WO + W CONT (Order #216928898) on 6/13/2018 - Order Result History Report

Signing Information

A preliminary report has been dictated and approved by ANTHONY ZBACNIK MD on Wed Jun 13, 2018 2:23:41 PM CDT

Image(s) reviewed and final report confirmed by STEPHEN A QUINET MD on Wed Jun 13, 2018 3:47:54 PM EDT

Reading physician

STEPHEN A QUINET, MD

ANTHONY P ZBACNIK, MD

PACS Images

Show images for MR BRAIN WO + W CONT

Scanned Documents - Results, Orders, Documentation

History, Radiology - Scan on 6/13/2018 1:38 PM by Pupak, Susan M, RTR : mri

Hard Copy Result Report

Open Hard Copy Result Report (Order #216928898 - MR BRAIN WO + W CONT)

Reviewed By List

Connelly, Jennifer M, MD on 6/13/2018 16:29

Connelly, Jennifer M, MD on 6/13/2018 16:29

Patient Release Status:

This result is not viewable by the patient.

Order

MR BRAIN WO + W CONT [70553.000] (Accession# FH0149-061318) (Order# 216928898)
MR RCBV SEQUENCE [76498.003] (Accession# FH0148-061318) (Order# 216928899)

Patient Information

Patient Name	Sex	DOB
Prosser, Anniken S (10790724)	Female	10/10/1983

Service Location

Name	Address	Phone
FROEDTERT & THE MEDICAL COLLEGE OF WISCONSIN	9200 W Wisconsin Ave Milwaukee WI 53226	414-805-3000

Performed Date/Time

DOS Time
Jun 13, 2018 12:52 PM

Order Providers

Authorizing Provider	Authorizing Provider Dept	Encounter Provider
JENNIFER CONNELLY MD, MD	NEUROSCIENCES CC	JENNIFER CONNELLY MD, MD

Order Information

Date of Service	Ordering User	Ordered As
6/13/2018 (13:34)	JENNIFER CONNELLY MD, 0000 MD	NORMAL

Results

MR BRAIN WO + W CONT [70553.000] (Accession#
FH0232-031518) (Order# 209170296)
MR RCBV SEQUENCE [76498.003] (Accession#
FH0231-031518) (Order# 209170298)

PACS Images

Show images for MR BRAIN WO + W CONT

Study Result

Exam: MR BRAIN WO + W CONT [70553.000] Service Date:
3/15/18

Impression:

1. Postoperative changes in the left temporal region are similar to the prior study. Linear enhancement at the posterior medial margin of the left anterior temporal resection cavity similar to the prior study.
2. An area of nonenhancing abnormal long TR signal with gyral expansion in the left lateral and medial temporal lobes and in the left subinsular region, similar to the prior study. No new lesions.
3. No evidence for abnormal vascularity on MR perfusion study.

Narrative:

Examination:

1. MRI of the brain without and with contrast.
2. MR perfusion study with contrast.

Clinical information: 34-year-old female status postop left temporal GBM.

Comparison: 12/14/2017.

Technique: Multisequence, multiplanar MR imaging of the brain was performed without and with contrast. Postcontrast imaging was performed after the intravenous injection of 6 mL Gadavist. An additional 6 mL of Gadavist were administered for MR perfusion study.

Findings:

Postoperative changes from prior left temporal craniotomy are again seen. An anterior left temporal resection cavity is seen, similar in size and appearance to the prior study. Linear enhancement at the posteromedial margin of the resection cavity is again seen, similar to the prior study. There is no definite nodular enhancement. Elsewhere along the resection cavity, no abnormal enhancement is seen.

No areas of abnormal vascularity are noted on MR perfusion study.

Gyral expansion and nonenhancing abnormal long TR signal involving the left lateral and medial temporal lobes and the left subinsular region is again noted, similar in extent to the prior study. No new lesions are identified.

Brain parenchymal volume is appropriate for the patient's age. No acute or subacute infarcts are seen. No acute intracranial hemorrhage or extra-axial fluid collections are seen. Areas of susceptibility in the operative bed are unchanged. Scattered foci of chronic microhemorrhage are seen in the brain parenchyma, more numerous on the left side, likely posttreatment. There is no hydrocephalus. No midline shift is seen and the basal cisterns are patent. Major intracranial flow voids are present.

Minor scattered sinus mucosal disease is seen. Orbits and mastoids are unremarkable.

Result History

MR BRAIN WO + W CONT (Order #209170296) on 3/15/2018 - Order Result History Report

Signing Information

A preliminary report has been dictated and approved by MOHIT AGARWAL MD on Thu Mar 15, 2018 1:38:50 PM CDT

Image(s) reviewed and final report confirmed by MOHIT AGARWAL MD on Thu Mar 15, 2018 2:07:01 PM CDT

Reading physician

MOHIT AGARWAL, MD

PACS Images

Show images for MR BRAIN WO + W CONT

Scanned Documents - Results, Orders, Documentation

History, Radiology - Scan on 3/15/2018 12:23 PM by Mercier, Gretchen A, RTR : MRI HISTORY

Scanned Documents - Results, Orders, Documentation

History, Radiology - Scan on 3/15/2018 12:23 PM by Mercier, Gretchen A, RTR : MRI HISTORY

Hard Copy Result Report

Open Hard Copy Result Report (Order #209170296 - MR BRAIN WO + W CONT)

Prosser, Anniken S

MRN: 10790724
Description: 34 year old female

Progress Notes Encounter Date: 3/15/2018

Connelly, Jennifer M, MD

Neurology

Neuro-Oncology followup Visit

RE: Anniken S Prosser

MR#: 10790724

DOB: 10/10/1983

Date of Clinic Visit: 3/15/2018

Chief Complaint: GBM

History of Present Illness:

Ms. Prosser is a 34 Y/o lady who returns to the Neuro-Oncology clinic for further evaluation and management of a left temporal Grade 4 astrocytoma. She comes to clinic today with her husband and son, Liam. Since her last visit, she has remained on TTFields (compliance 91% for march). She is using clobetasol as needed. They rotate around open lesions. Neurologically, she is doing great with no other symptoms. She has otherwise been healthy.

Neuro-oncology History:

H/o migraines - started in mid-20's; possibly secondary to Crohn's meds; diffuse in nature and daily

Feb. 14, 2016 - intractable migraine

MRI - large left cystic temporal mass

Feb. 25, 2016 - left craniotomy - GBM

May 2016 - completed radiation with Dr. Editha Kruegar with concurrent temodar with Dr. Jasleen Randhawa

June 2016 - continue with adjuvant temodar

June 16, 2016 - started Optune TTFields

April 2017 - completed 12 cycles of temodar; continue TTFields

Past Medical History:

Diagnosis	Date
• Crohn's disease (*)	
• GBM (glioblastoma multiforme)	2/25/16
left temporal	
• WPW (Wolff-Parkinson-White syndrome) 1999	
s/p ablation	

Social History

Social History

• Marital status:	Married
Spouse name:	N/A
• Number of children:	N/A
• Years of education:	N/A

Social History Main Topics

- | | |
|----------------------|--------------|
| • Smoking status: | Never Smoker |
| • Smokeless tobacco: | Never Used |
| • Alcohol use | Not on file |
| • Drug use: | Unknown |
| • Sexual activity: | Not on file |

Other Topics

- Not on file

Concern

Social History Narrative

- No narrative on file

Family History

Problem	Relation	Age of Onset
• Breast Cancer	Maternal Aunt	
• Ovarian Cancer onset in 20's	Maternal Cousin	
• Cancer onset in 80's - leukemia	Paternal Grandfather	

Current Outpatient Prescriptions

Medication	Sig
• acetaminophen (TYLENOL) 500 MG tablet	Take 500 mg by mouth every 4 hours as needed.
• Calcium Citrate-Vitamin D (CALCIUM + D PO)	Take 1 tablet by mouth daily.
• clobetasol propionate (CLOBEVATE OR - - TEMOVATE) 0.05 % cream	Apply as needed to scalp rash. Leave on for 20-60 minutes, cleanse lightly with alcohol and apply arrays.
• fish oil	Take 1 tablet by mouth daily.
• Multiple Vitamins-Minerals (WOMENS DAILY MULTIVITAMIN PO)	Take 1 tablet by mouth daily.
• NON FORMULARY MEDICATION	Reasonsreishi mushroom for immune support
• TURMERIC CURCUMIN PO	Take 1 tablet by mouth daily. Patient uses brand Curcubrain

Allergies

Allergen	Reactions
• Ragweed	EENT - watery eyes
• Sulfa Drugs	RESP - shortness of breath

ROS:

Constitutional - denies fevers, weight loss
Eyes - denies diplopia

Ears, Nose, Mouth, Throat - denies difficulty swallowing
Cardiovascular - denies chest pain
Respiratory - denies SOB, cough
Gastrointestinal - has constipation intermittently while on temodar, this balances the diarrhea caused by Crohns
Genitourinary - denies dysuria
Integumentary - has skin breakdown in scalp
Neurological - as per HPI
Psych - denies depression, anxiety

Exam:

Vitals:

03/15/18 1429
BP: 129/87
Pulse: 85
Resp: 16
Temp: 98.2 °F (36.8 °C)
SpO2: 98%
Weight: 51.8 kg (114 lb 3.2 oz)

General: no distress.
Skin: mild contact dermatitis

Neurologic:

Mental Status: Alert and attentive. Oriented to person, place, time and reason for visit. Language fluent with intact comprehension. Immediate recall, working memory, and long-term memory intact. No neglect.

Cranial Nerves:

- 1 - not assessed
- 2 - Fully intact visual fields bilaterally via confrontation.
- 3, 4, 6 - extraocular movements intact and conjugate. Normal smooth pursuit. Normal saccades.
- 5 - normal facial sensation to light touch bilaterally.
- 7 - symmetric facies with normal smile, palpebral fractures, nasal labial folds and forced eyelid closure.
- 8 - grossly intact
- 9, 10 - symmetric palate elevation.
- 11 - 5/5 head turning, bilaterally.
- 12 - tongue midline at rest and upon protrusion.

Motor: 5/5 throughout with normal bulk and tone; no evidence of pronation
Finger tapping: normal frequency and amplitude bilaterally

Reflexes: 2+ throughout

Sensation: Intact to light touch in all 4 extremities

Motor Integration (Cerebellar):

Finger to Nose: Normal bilaterally without ataxia, dysmetria, or tremor.
Rapid Alternating Movements: Normal with bilateral hands

Gait:

Prosser, Anniken S (MR # 10790724) Printed by Guzlecki, Carrie A, RN [27113] at 5/29/... Page 4 of 4
Case 1:20-cv-00194-WCG Filed 04/28/20 Page 57 of 539 Document 11-6 4919

novocure

Patient Compliance Report

Patient Name: Anniken Prosser

Treating Physician: Dr. Jennifer Connelly

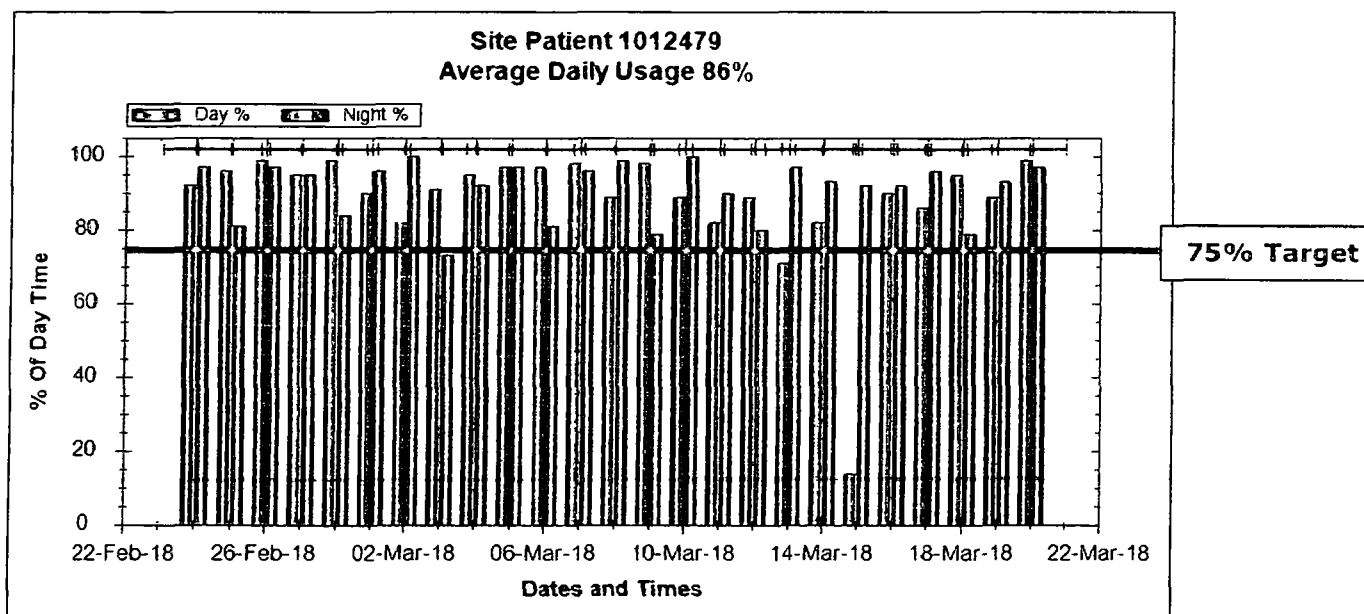
Treating Institution: Froedtert Hospital and the Medical College of Wisconsin

Novocure Patient Number: 1012479

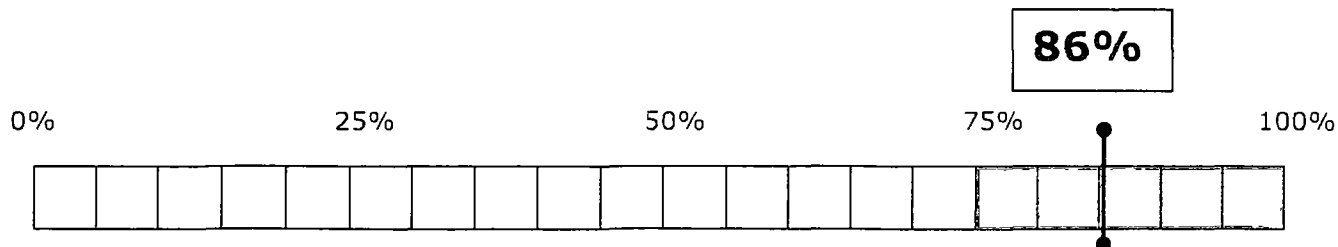
Report Date: March 21, 2018

Period Covered: February 24, 2018 – March 20, 2018

Average Daily Usage:



Overall Compliance for the Period:



Report compiled by: Danita Ziegler

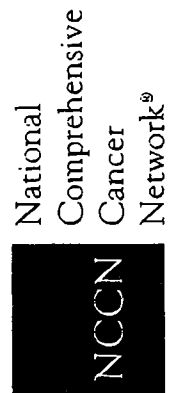
NCCN Clinical Practice Guidelines in Oncology
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Central Nervous System Cancers

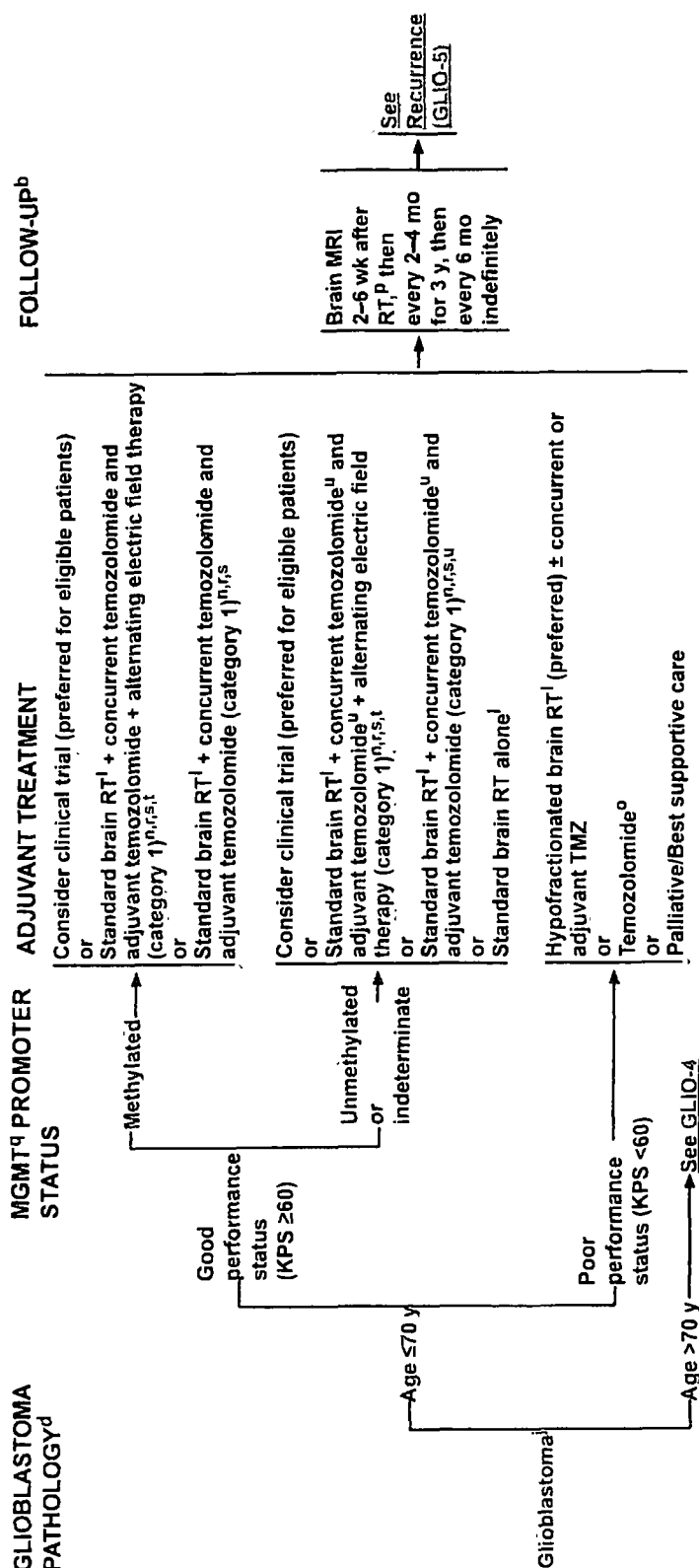
Overall management of Central Nervous System Cancers from diagnosis through recurrence is described in the full NCCN Guidelines® for Central Nervous System Cancers. Visit NCCN.org to view the complete library of NCCN Guidelines.

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Anaplastic Gliomas^a/Glioblastoma



^aThis pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
^bSee Principles of Brain and Spine Tumor Imaging (BRIN-A).
^cSee Principles of Brain Tumor Pathology (BRIN-F).
^dThis pathway also includes gliosarcoma.
^eSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRIN-C).
^fSee Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRIN-D).
^gConsider temozolomide if tumor is MGMT promoter methylated.
^hWithin the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
ⁱMGMT = O⁶-methylguanine-DNA methyltransferase.
^jCombination of agents may lead to increased toxicity or radiographic changes.
^kBenefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown.
^lAlternating electric field therapy is only an option for patients with supratentorial disease.
^mClinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.

All recommendations are category 2A unless otherwise indicated.
 Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GLIO-3

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GLIOBLASTOMA PATHOLOGY^d **MGMT PROMOTER STATUS^q** **ADJUVANT TREATMENT** **FOLLOW-UP^b**

↓

Good performance status (KPS ≥60) →

 Methylated →

 Consider clinical trial (preferred for eligible patients)
 or
 Hypofractionated brain RT¹
 + concurrent and adjuvant temozolomide (category 1)^{n,r,s}
 or
 Standard RT¹ + concurrent temozolomide and adjuvant temozolomide +
 alternating electric field therapy (category 1)^{n,r,s,t}
 or
 Standard RT¹ + concurrent temozolomide and adjuvant temozolomide^{n,r,s}
 or
 Temozolomide
 or
 Hypofractionated brain RT alone¹

 Unmethylated
 or
 Indeterminate →

 Consider clinical trial (preferred for eligible patients)
 or
 Hypofractionated brain RT¹
 + concurrent and adjuvant temozolomide^{n,r,s}
 or
 Standard RT¹ + concurrent temozolomide^u and adjuvant temozolomide^u
 + alternating electric field therapy (category 1)^{n,r,s,t}
 or
 Standard RT¹ + concurrent temozolomide^u and adjuvant temozolomide^{n,r,s,u}
 or
 Hypofractionated brain RT alone¹

↓

Poor performance status (KPS <60) →

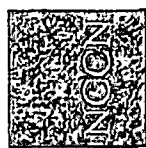
 Hypofractionated brain RT alone¹
 or
 Temozolomide^o
 or
 Palliative/Best supportive care

 ↓

 Recurrence (GLIO-5)
 See
 Brain MRI
 2-6 wk after
 RT¹, then
 every 2-4 mo →
 for 3 y, then
 every 6 mo
 indefinitely

All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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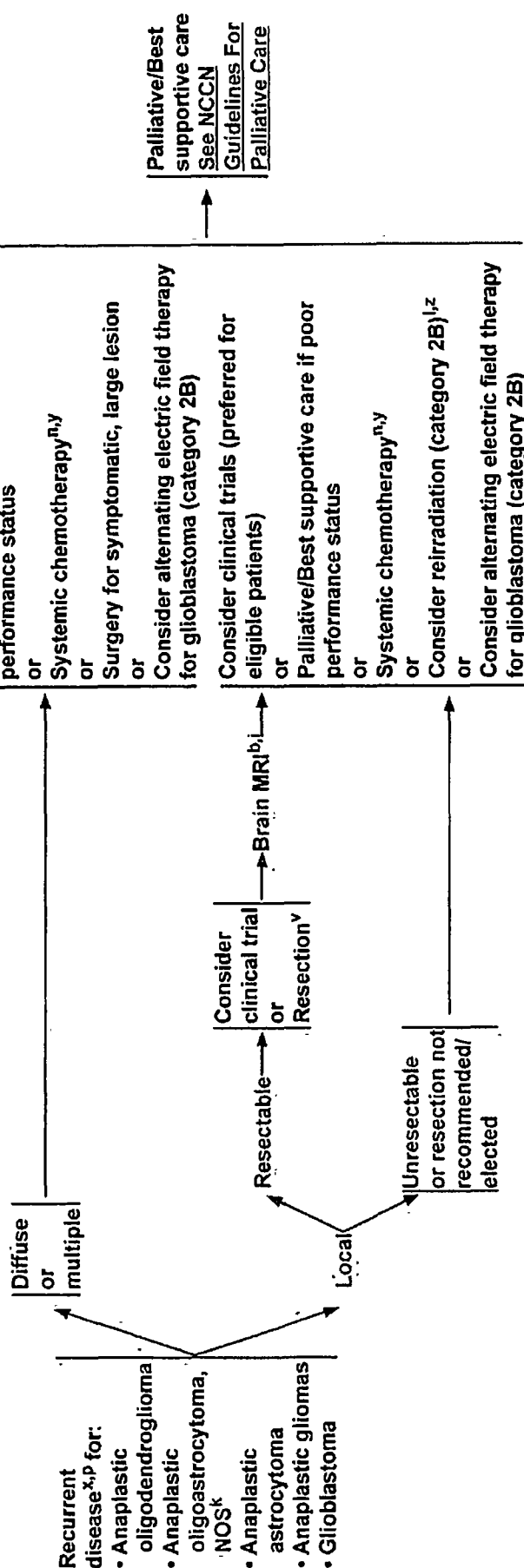


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NCCN Guidelines Version 1.2018 **Anaplastic Gliomas^a/Glioblastoma**

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

RECURRENCE



^aThis pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.

^bSee Principles of Brain and Spine Tumor Imaging (BRAIN-A).

^cPostoperative brain MRI within 24–72 hours after surgery.

^kThe 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although “anaplastic oligoastrocytoma, NOS” may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.

^lSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

ⁿSee Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

^wWithin the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.

^vConsider camustine (BCNU) wafer implant during resection. Treatment with camustine wafer may impact enrollment in clinical trials.

^xThe efficacy of standard-of-care treatment for recurrent glioblastoma is suboptimal, so for eligible patients consideration of clinical trials is highly encouraged. Prior treatment may impact enrollment in clinical trials.

^yConsider biopsy, MR spectroscopy, MR perfusion, brain PET/CT, or brain PET/MRI, or re-image to follow changes that may be due to progression versus radionecrosis.

^zAnaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.

^zEspecially if long interval since prior RT and/or if there was a good response to prior RT.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GLIO-5

Research

JAMA Oncology | Original Investigation

Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma

A Secondary Analysis of a Randomized Clinical Trial

Martin J. B. Taphoorn, MD; Linda Dirven, PhD; Andrew A. Kanner, MD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Sophie Taillibert, MD; Steven A. Toms, MD; Jerome Honnorat, MD, PhD; Thomas C. Chen, MD, PhD; Jan Sroubek, MD; Carlos David, MD; Ahmed Idbaih, MD, PhD; Jacob C. Easaw, MD, PhD; Chae-Yong Kim, MD, PhD; Jordi Bruna, MD, PhD; Andreas F. Hottinger, MD, PhD; Yvonne Kew, MD, PhD; Patrick Roth, MD; Rajiv Desai, MD; John L. Villano, MD, PhD; Eilon D. Kirson, MD, PhD; Zvi Ram, MD; Roger Stupp, MD

 Invited Commentary

 Supplemental content

IMPORTANCE Tumor-treating fields (TTFields) therapy improves both progression-free and overall survival in patients with glioblastoma. There is a need to assess the influence of TTFields on patients' health-related quality of life (HRQoL).

OBJECTIVE To examine the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS This secondary analysis of EF-14, a phase 3 randomized clinical trial, compares TTFields and temozolomide or temozolomide alone in 695 patients with glioblastoma after completion of radiochemotherapy. Patients with glioblastoma were randomized 2:1 to combined treatment with TTFields and temozolomide or temozolomide alone. The study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

INTERVENTIONS Temozolomide, 150 to 200 mg/m²/d, was given for 5 days during each 28-day cycle. TTFields were delivered continuously via 4 transducer arrays placed on the shaved scalp of patients and were connected to a portable medical device.

MAIN OUTCOMES AND MEASURES Primary study end point was progression-free survival; HRQoL was a predefined secondary end point, measured with questionnaires at baseline and every 3 months thereafter. Mean changes from baseline scores were evaluated, as well as scores over time. Deterioration-free survival and time to deterioration were assessed for each of 9 preselected scales and items.

RESULTS Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months; $P < .01$); physical (5.1 vs 3.7 months; $P < .01$) and emotional functioning (5.3 vs 3.9 months; $P < .01$); pain (5.6 vs 3.6 months; $P < .01$); and leg weakness (5.6 vs 3.9 months; $P < .01$), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse: 8.2 vs 14.4 months; $P < .001$) and pain (TTFields improved; 13.4 vs 12.1 months; $P < .01$). Role, social, and physical functioning were not affected by TTFields.

CONCLUSIONS AND RELEVANCE The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00916409

JAMA Oncol. doi:10.1001/jamaoncol.2017.5082
Published online February 1, 2018.

Author Affiliations: Author affiliations are listed at the end of this article

Corresponding Author: Martin J. B., Taphoorn, MD, PhD, Department of Neurology, Haaglanden Medical Center, PO BOX 2191, 2501 VC, The Hague, The Netherlands (m.taphoorn@haaglandenmc.nl).

Glioblastoma has a poor prognosis,^{1,2} and, as tumors grow, patients often experience a progressive decline in neurologic function and health-related quality of life (HRQoL).³⁻⁷ The current standard of care is not curative but results in prolongation of life. However, extension of survival is meaningful only if patients' functioning and well-being can be retained or improved.⁸⁻¹¹ Therefore, it is important to determine the net clinical benefit of each new treatment or treatment modality introduced; possible benefits of a new treatment, in terms of prolonged survival, have to be carefully weighed against potential negative effects of the treatment on the patients' quality of life.

The current standard of care for patients with newly diagnosed glioblastoma comprises surgical resection to the extent safely feasible followed by radiotherapy with concomitant and maintenance chemotherapy with temozolomide.¹² Tumor-treating fields (TTFields) (Optune; Novocure Ltd) is an antimitotic physical treatment modality^{13,14} delivered by a home use medical device with wired transducer arrays placed on the patients' scalp. When added to standard maintenance temozolomide chemotherapy, TTFields has been demonstrated to improve both progression-free survival and overall survival in a randomized clinical trial (NCT00916409).¹⁵

Treatment with TTFields involves the patient carrying a mobile electrical device for more than 18 hours per day and having 4 arrays of transducers continuously fixed to the shaved scalp. Concerns regarding the influence of wearing the device on patients' HRQoL have therefore been raised.^{16,17} The incidence of adverse events was not increased by the addition of TTFields to temozolomide therapy except for an expected mild to moderate skin irritation beneath the electrodes in 52% of patients (severe in 2%). Herein, we report on the influence of treatment with TTFields on the patients' HRQoL, which was a predefined secondary objective of the randomized clinical trial. The present study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

Methods

Study Population

Patients eligible for this study were aged 18 years or older, had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma), were progression free after undergoing maximal safe debulking surgery or biopsy, and had completed standard radiotherapy with concomitant temozolomide. Patients were required to have a Karnofsky Performance Status score of at least 70 at the time of enrollment, corresponding to at least being able to perform self-care. Further details on the study population are available elsewhere.¹⁵ All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centers and the relevant competent authorities (eAppendix 1 in Supplement 1); the participants did not receive financial compensation.

Key Points

Question What is the influence of adding tumor-treating fields to the standard treatment on health-related quality of life in patients with glioblastoma?

Findings In this secondary analysis of the EF-14 randomized clinical trial, the addition of tumor-treating fields did not negatively influence health-related quality of life except for itchy skin, an expected consequence from the transducer arrays.

Meaning Tumor-treating field therapy has previously been shown to prolong both progression-free and overall survival. When considering the net clinical benefit, improved survival without a negative influence on health-related quality of life supports the addition of tumor-treating fields to standard treatment in patients with glioblastoma.

Study Design and Treatment

This prospective, multicenter, open-label, randomized clinical phase 3 trial recruited 695 patients at 90 medical centers in North America, Europe, the Republic of Korea, and Israel. The trial protocol is available in Supplement 2. The trial was designed to test the efficacy of TTFields in combination with the best standard of care in the treatment of newly diagnosed glioblastoma (ie, radiotherapy with concomitant and adjuvant temozolomide). The primary end point was progression-free survival, with overall survival as a powered secondary end point. Health-related quality of life was a secondary end point. Patients who were progression free after completion of radiochemotherapy were randomized within 4 to 7 weeks at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m² for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. If tolerated well, TTField therapy was to be continued until the second progression or up to 2 years.

Patients in the TTFields plus temozolomide group received continuous TTFields combined with maintenance temozolomide. TTFields were delivered through a portable device in an outpatient setting. Patients receiving TTFields had 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain. Although uninterrupted treatment was recommended, the patient could take short breaks if needed; patients were advised to continue treatment for at least 18 hours a day. More details on the study design and treatment are published elsewhere.¹⁵

HRQoL Assessment

The evaluation of HRQoL was performed using the validated European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) and brain module (QLQ-BN20).¹⁸⁻²⁰ Questionnaires were completed on paper at baseline (prior to randomization) and subsequently every 3 months for up to 12 months. Nine scales and items were preselected as important based on relevance for patients with glioblastoma and hypothesized effects of the TTFields delivery device on patients' HRQoL: global health status; physical, cognitive, role, social, and emotional functioning; itchy skin;

pain; and weakness of legs. We hypothesized that any burden of carrying the device (on physical functioning and itchy skin) or detriment to social and role functioning due to the visibility of the therapy may be balanced by patients' feeling of well-being (global health status and emotional functioning) related to active participation of both the patient and the caregiver in the fight against cancer and increasing patient empowerment. Moreover, we hypothesized that treatment with TTFields would not have an influence on cognitive functioning, pain, and weakness of legs.

Statistical Analysis

Calculation of HRQoL Scores

The items on both questionnaires were scaled and scored using the recommended EORTC procedures.²¹ Raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. The results of this study are presented in accordance with guidelines for reporting HRQoL in cancer clinical trials and methods.²²⁻²⁴ Differences of at least 10 points (on a 0-100 scale) were classified as the minimum clinically meaningful change in any HRQoL scale/item.²⁴

Descriptive Statistics

Descriptive statistics were used to report HRQoL scores as well as the sociodemographic and clinical variables for the population of patients who completed at least 1 HRQoL scale at baseline separately for both treatment groups. Means and SDs or medians and ranges were calculated for continuous variables depending on the distribution of the variable. Frequencies and percentages were calculated for nominal variables. Differences between arms were tested using a 2-sided χ^2 test or an independent 2-tailed, unpaired *t* test or Mann-Whitney test at an α value of .05 for each variable.

Adherence to HRQoL assessments was calculated as the number of forms received divided by the number of forms expected at every assessment. Patients who completed the assessments at the time of progression were included in this analysis.

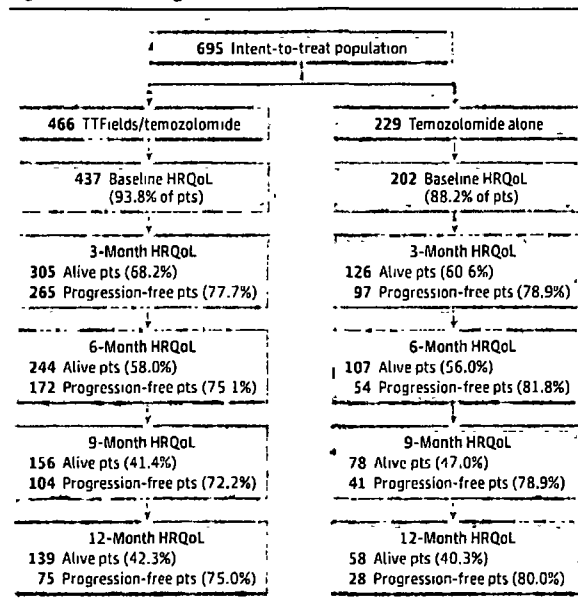
HRQoL Scores Over Time

Mean HRQoL scores over time were calculated as well as the mean changes from baseline. A stable HRQoL score was defined as a change of less than 10 points, and a change of 10 or more points indicated a deterioration or improvement depending on the scale or item. Mean change from baseline was plotted to evaluate the longitudinal course of patients' experience of disease and treatment, and a linear mixed-model repeated-measures analysis was used to estimate the treatment effect over time. A sensitivity analysis of complete cases using multiple imputations with a predictive mean matching regression model was used to check the robustness of the treatment effect over time. An additional sensitivity analysis used a repeated-measures model that assumes there is random variation among participants that is related to the time of dropout.

Stable or Improved HRQoL During the Progression-Free Period

The percentage of patients with stable (<10-point change) or improved (≥ 10 -point change) HRQoL during the progression-

Figure 1. Consort Diagram



Data are the number and percentage of patients in the categories (baseline, alive, and progression-free) who completed the health-related quality-of-life (HRQoL) questionnaire at the indicated times. pts indicates patients. TTFields, tumor-treating fields.

free period, thus excluding the HRQoL assessment at progression, was determined separately for both treatment arms. This calculation was based on the total number of patients with a valid baseline HRQoL assessment and at least 1 additional follow-up assessment. Moreover, the area under the curve of stable or improved HRQoL for the entire duration of stability or improvement was determined, and differences between arms were assessed with the trapezoidal method (eAppendix 2 in Supplement 1).

Deterioration-Free Survival and Time to Deterioration

Deterioration-free survival was defined as the time to a greater than 10-point deterioration in scores from baseline without a subsequent 10-point or more improvement in scores compared with baseline, progressive disease, or death in the absence of a previous definitive deterioration before the next assessment. Disease progression was included as a surrogate measure. Data were censored at the last HRQoL assessment date for patients with a change of less than 10 points, patients who did not progress, or patients who died after 9 weeks since the last assessment. Data for patients with missing baseline scores were not included, and patients missing all postbaseline HRQoL assessments were censored at randomization. Time to deterioration (TTD) was defined similarly to deterioration-free survival, with the exception that progressive disease was excluded as an event (ie, nonmissing HRQoL data beyond progression were included). Kaplan-Meier methodology was used to estimate deterioration-free survival and TTD distributions and median times, and 95% CIs were computed using the Greenwood formula. The difference between treatment arms

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	TTFields Plus Temozolomide (n = 437)	Temozolomide (n = 202)	All Patients (N = 639)	P Value
Age, y				
Mean (SD)	54.6 (11.4)	55.2 (11.6)	54.8 (11.5)	.50
Median (range)	56.0 (19-83)	57.0 (19-80)	56.0 (19-83)	
Sex, No. (%)				
Male	297 (68.0)	140 (69.3)	437 (68.4)	
Female	140 (32.0)	62 (30.7)	202 (31.6)	.73
Antiepileptic medication at baseline, No. (%)	174 (39.8)	79 (39.1)	253 (39.6)	.87
Corticosteroid therapy at baseline, No. (%)	129 (29.5)	60 (29.7)	189 (29.6)	.96
Region, No. (%)				
United States	203 (46.5)	97 (48.0)	300 (46.9)	
Canada, Europe, Israel, and Korea	234 (53.5)	105 (52.0)	339 (53.1)	.71
Extent of resection, No. (%)				
Biopsy	55 (12.6)	24 (11.9)	79 (12.4)	
Partial resection	149 (34.1)	70 (34.7)	219 (34.3)	.97
Gross total resection	233 (53.3)	108 (53.5)	341 (53.4)	
Tumor position, No. (%) ^a				
Corpus callosum	23 (5.3)	12 (5.9)	35 (5.5)	
Frontal lobe	177 (40.5)	74 (36.6)	251 (39.3)	
Occipital lobe	55 (12.6)	24 (11.9)	79 (12.4)	.66
Parietal lobe	138 (31.6)	78 (38.6)	216 (33.8)	
Temporal lobe	179 (41.0)	81 (40.1)	260 (40.7)	
Missing	2 (<1)	2 (1.0)	4 (0.6)	
Tumor location, No. (%) ^a				
Left	202 (46.2)	84 (41.6)	286 (44.8)	
Right	234 (53.5)	116 (57.4)	350 (54.8)	.65
Both	4 (0.9)	2 (1.0)	6 (0.9)	
Corpus callosum	14 (3.2)	9 (4.5)	23 (3.6)	
Completed radiotherapy, No. (%)				
<57 Gy	20 (4.6)	10 (5.0)	30 (4.7)	
60 Gy (standard, $\pm 5\%$)	399 (91.3)	188 (93.1)	587 (91.9)	.38
>63 Gy	15 (3.4)	3 (1.5)	18 (2.8)	
Missing	3 (0.7)	1 (0.5)	4 (0.6)	
Karnofsky performance score				
Median (range)	90 (60-100)	90 (70-100)	90 (60-100)	.26
Baseline Mini-Mental State Examination score available, No. (%)				
≤ 26	81 (18.9)	43 (22.2)	124 (19.9)	
27-30	348 (81.1)	151 (77.8)	499 (80.1)	.34
Cycles (months) of treatment with TTFields		NA	NA	NA
No.	425			
Mean (SD)	12.5 (11.8)			
Median (range)	8.3 (0-82)			
Cycles of treatment with temozolomide				
No.	430	192	622	
Mean (SD)	8.9 (8.3)	7.5 (6.2)	8.5 (7.8)	.02
Median (range)	6.2 (0-51)	5.5 (0-33)	5.9 (0-51)	
Adherence to TTFields therapy ^b	327 (74.8)	NA	NA	NA

Abbreviations: Gy, gray; NA, not applicable; TTFields, tumor-treating fields.

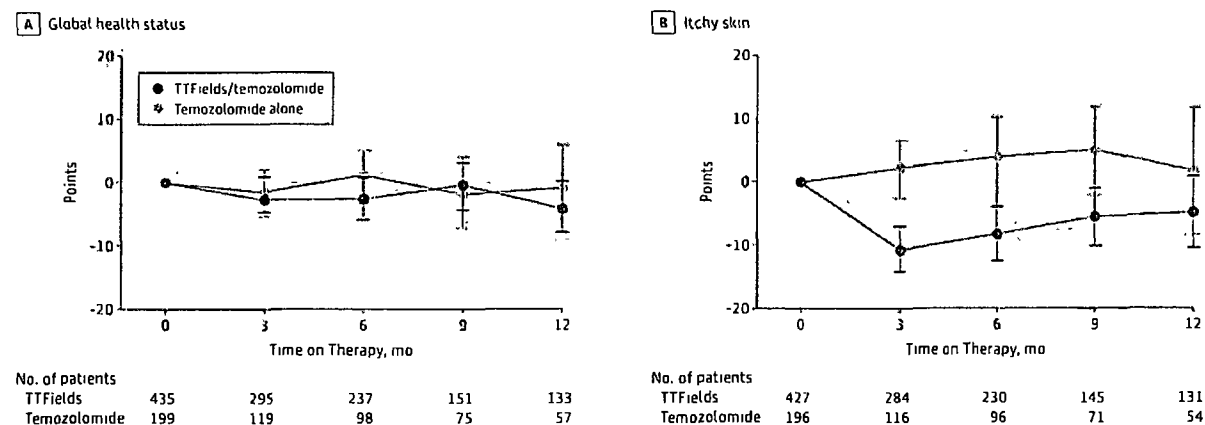
^a Multiple locations possible.

^b Defined as use of the device 75% or more of the time during the first 3 months of treatment.

was compared using a 2-sided stratified log-rank test. Hazard ratios were estimated using a stratified (for extent of resection and *MGMT* status) Cox proportional hazards regression model.

SAS, version 9.4 (SAS Institute) was used for all statistical analyses, and comparisons between groups were based on the intent-to-treat principle. *P* values < .05 were considered to be

Figure 2. Changes in Global Health Status and Itchy Skin



Mean changes in points on health-related quality of life scales from baseline in global health status (A) and itchy skin with (B) with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. No change,

between 0 and 10 points; improvement and deterioration, changes of 10 points or more. Error bars indicate SD.

statistically significant. The Hochberg procedure was used to adjust for the multiplicity of treatment comparisons in the pre-selected HRQoL scales analyses.

Results

Patients

A total of 695 patients were randomly assigned in a 2:1 ratio to TTFields plus temozolomide ($n = 466$) or temozolomide alone ($n = 229$). A total of 639 (91.9%) patients completed at least 1 HRQoL scale at baseline: 437 (93.8%) of those in the TTFields plus temozolomide arm and 202 (88.2%) patients in temozolomide-alone arm (Figure 1). The baseline demographics of the patients who provided HRQoL data were comparable to those of the intention-to-treat population¹⁵ and were well balanced between treatment arms in this subpopulation (Table 1).

HRQoL Completion Rates and Baseline Scores

Adherence to HRQoL assessments decreased from 91.9% at baseline to 65.8% (431 of 655 patients alive) at 3 months and dropped to 41.7% (197 of 473 patients alive) at 12 months of follow-up (Figure 1). Mean and median baseline HRQoL scores were comparable between arms for all preselected scales/items (eTable 1 in Supplement 1), as well as the exploratory scales and items. Reference values of HRQoL scores of a healthy general population²⁵ were available for 7 of 9 predefined scales and items (except itchy skin and weakness of legs). Patients with glioblastoma after completion of radiochemotherapy showed clinically relevant worse functioning or more symptoms compared with the general population on all scales except pain, which was similar.²⁵

Mean Changes in HRQoL From Baseline and the Repeated-Measures Mixed-Effect Model

Mean changes in HRQoL over time for the global health status is presented in Figure 2A and for all 9 predefined HRQoL scales

in the eFigure in Supplement 1. Throughout the 12-month assessment period, mean changes from baseline were stable (<10 -point change from baseline) for all 9 predefined HRQoL scales in both treatment arms (eFigure in Supplement 1) with the exception of itchy skin (Figure 2B). For itchy skin, a clinically relevant deterioration (ie, an increase in itchy skin) compared with baseline was seen at the month 3 evaluation in the TTFields plus temozolomide arm (mean [SD] increase, 10.4 [30.1] points vs an improvement of 2.3 [24.4] points in the temozolomide arm). For differences between treatment arms, patients treated with TTFields plus temozolomide had significantly and clinically relevant worse itchy skin at 3, 6, and 9 months than patients treated with temozolomide alone, but not at 12 months (mean [SD] increase of 10.4 [30.1] in the TTFields plus temozolomide arm vs a decrease of 2.3 [24.4] in the temozolomide-alone arm, $P = .005$; increase of 8.1 [31.6] in the TTFields plus temozolomide arm vs a decrease of 4.2 [31.4] in the temozolomide-alone arm, $P = .008$; increase of 5.3 [28.0] in the TTFields plus temozolomide arm vs a decrease of 5.2 [29.6] in the temozolomide-alone arm, $P = .04$; increase of 4.6 [32.8] in the TTFields plus temozolomide arm vs a decrease of 1.9 [36.9] in the temozolomide-alone arm, $P = .66$, respectively). For all other scales, there were no statistically significant or clinically relevant differences between treatment arms.

The repeated-measures mixed-effect model supported this finding, with no statistically significant difference between treatment arms in HRQoL scores over time in any predefined scale or item except for itchy skin ($P < .001$), which was worse in the TTFields plus temozolomide arm (eTable 2 in Supplement 1). The sensitivity analyses showed that the results of the linear mixed model were robust.

Stable or Improved HRQoL During Progression-Free Time
Compared with baseline, more patients in the TTFields plus temozolomide arm compared with the temozolomide-alone arm reported stable or improved scores for global health status (53.5% vs 38.0%, respectively, $P = .001$), physical func-

Table 2. Stable or Improved Health-Related Quality of Life During Progression-Free Time

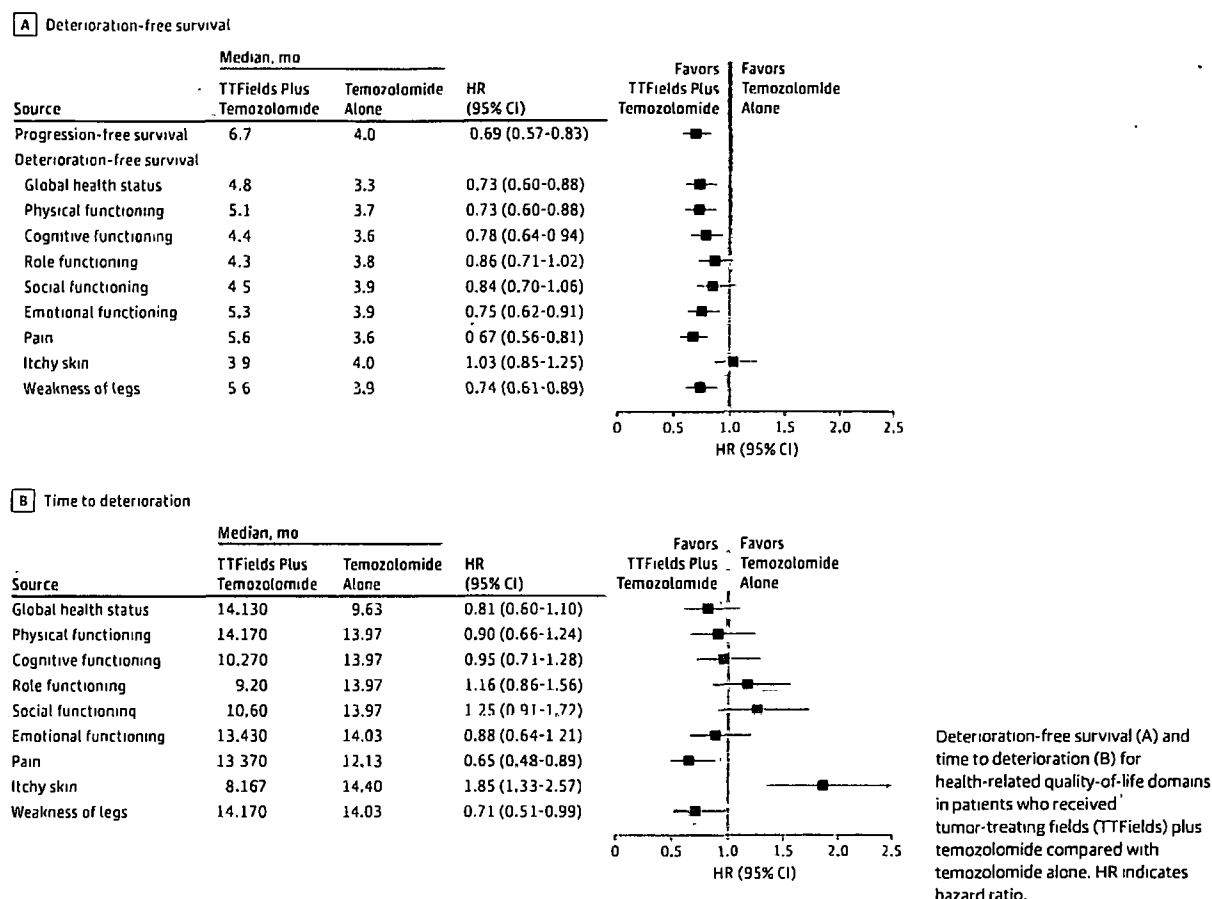
Characteristic	TTFields Plus Temozolomide (n = 361)	Temozolomide (n = 142)	P Value	α Value
Pain				
Stable/improved from baseline, No./No. (%)	205/361 (56.8)	51/142 (35.9)	<.001	.05
Median duration (95% CI), mo	6.2 (5.9 to 7.0)	6.3 (5.6 to 9.1)	.88	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (0 to 0)	.80	
Global health status				
Stable/improved from baseline, No./No. (%)	192/359 (53.5)	53/141 (37.6)	.001	.025
Median duration (95% CI), mo	6.3 (5.9 to 7.4)	7.9 (5.9 to 9.8)	.24	
Median CFB AUC until last stable/improved status (95% CI)	24.4 (11.9 to 35.0)	65.9 (13.1 to 121.3)	.13	
Physical functioning				
Stable/improved from baseline, No./No. (%)	195/361 (54.0)	54/142 (38.0)	.001	.017
Median duration (95% CI), mo	6.2 (5.9 to 8.2)	9.1 (5.9 to 9.8)	.21	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 18.7)	0 (0 to 30.0)	.53	
Weakness of legs				
Stable/improved from baseline, No./No. (%)	206/351 (58.7)	58/138 (42.0)	.001	.013
Median duration (95% CI), mo	6.3 (6.0 to 8.3)	9.1 (5.9 to 9.8)	.08	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (0 to 0)	.51	
Cognitive functioning				
Stable/improved from baseline, No./No. (%)	181/359 (50.4)	55/142 (38.7)	.02	.01
Median duration (95% CI), mo	6.0 (4.9 to 6.5)	6.2 (5.7 to 9.6)	.65	
Median CFB AUC until last stable/improved status (95% CI)	26.3 (0 to 48.6)	0 (0 to 93.3)	.37	
Emotional functioning				
Stable/improved from baseline, No./No. (%)	196/359 (54.6)	62/142 (43.7)	.03	.008
Median duration (95% CI), mo	6.3 (6.0 to 8.3)	7.7 (5.8 to 9.4)	.38	
Median CFB AUC until last stable/improved status (95% CI)	22.6 (5.8 to 35.0)	25.2 (0 to 54.4)	.73	
Social functioning				
Stable/improved from baseline, No./No. (%)	173/359 (48.2) *	58/142 (40.8)	.14	.007
Median duration (95% CI), mo	6.2 (5.9 to 7.1)	6.7 (5.9 to 9.6)	.40	
Median CFB AUC until last stable/improved status (95% CI)	16.5 (0 to 47.2)	0 (0 to 54.4)	.90	
Role functioning				
Stable/improved from baseline, No./No. (%)	173/361 (47.9)	58/141 (41.1)	.17	.006
Median duration (95% CI), mo	5.9 (4.4 to 6.3)	7.3 (5.7 to 9.3)	.27	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 25.0)	46.7 (0 to 75.8)	.34	
Itchy skin				
Stable/improved from baseline, No./No. (%)	148/349 (42.4)	64/137 (46.7)	.39	.0056
Median duration (95% CI), mo	6.0 (4.7 to 6.3)	6.7 (5.6 to 9.4)	.37	
Median CFB AUC until last stable/improved status (95% CI)	0 (0 to 0)	0 (-102.2 to 0)	.19	

Abbreviations: AUC, area under the curve; CFB, change from baseline; TTFields, tumor-treating fields.

tioning (54.0% vs 37.0%, respectively; $P = .001$), pain (56.8% vs 35.9%, respectively; $P < .001$), and weakness of legs (58.7% vs 42.0%, respectively; $P = .001$) but not in any of the other HRQoL scales and items. However, the duration of stable or improved HRQoL was shorter in the TTFields plus temozolomide arm, although not significantly different from the temo-

zolomide arm for any of the HRQoL scales and items. Overall, with a combination of these measures, the area under the curve analysis showed no significant differences between treatment arms for any of the HRQoL scales and items, indicating a similar HRQoL between treatment arms while patients did not experience tumor progression (Table 2).

Figure 3. Deterioration-Free Survival and Time to Deterioration



Deterioration-Free Survival and TTD

The addition of TTFields to standard temozolomide chemotherapy resulted in statistically significant longer deterioration-free survival in global health status, physical and emotional functioning, pain, and weakness of legs (Figure 3A and eTable 2 in Supplement 1); the significant difference remained after correction for multiple testing. When progression was removed as a deterioration event (TTD), there was no negative influence of TTFields plus temozolomide treatment on the TTD of HRQoL (Figure 3B) except for itchy skin, which was worse in the TTFields plus temozolomide arm (8.2 vs 14.4 months). In contrast, the addition of TTFields to temozolomide resulted in a statistically significant prolongation until deterioration for pain (13.4 vs 12.1 months, $P < .01$). There were no other significant differences in TTD between arms (Figure 3B).

Discussion

In our detailed analysis of HRQoL during therapy with TTFields in addition to temozolomide, no significant difference was found between the groups in patients' HRQoL over time except for the skin reaction. As expected, itchy skin was reported more frequently in patients treated with TTFields be-

cause of the transducer arrays that have to be placed on the scalp of the patient. Consistently, over half of the patients also reported skin irritation as an adverse event. We had hypothesized that patients treated with TTFields may have better HRQoL in some domains as a result of active participation in the fight against cancer and the frequent interactions between patients and caregivers and device technicians regarding the device. However, on a group level, global health status and emotional functioning were not significantly different between treatment arms. Likewise, our hypotheses that the addition of TTFields would result in worse role and social functioning (due to the visibility of the device) and worse physical functioning were not confirmed. In line with our hypotheses, cognitive functioning, pain, and weakness of legs were not negatively affected by the addition of TTFields to temozolomide treatment. Most relevant for patients, HRQoL was maintained (in 8 of 9 of the predefined scales/items) over time. Combining the results of the survival and HRQoL analyses suggests that the addition of TTFields to adjuvant temozolomide is of value to patients with glioblastoma.

Patients who received TTFields had significantly longer deterioration-free survival compared with those in the temozolomide-alone arm for global health status (4.8 vs 3.3 months; $P < .01$), physical (5.1 vs 3.7 months; $P < .01$) and

emotional functioning (5.3 vs 3.9 months; $P < .01$), pain (5.6 vs 3.6 months; $P < .01$), and weakness of legs (5.6 vs 3.9 months; $P < .01$). For the other scales and items, there was no significant difference in deterioration-free survival between the 2 treatment arms. The prolonged deterioration-free survival for these scales is explained by the extended progression-free survival for patients in the combined TTFields plus temozolomide arm, as progressive disease is included as an event in this analysis. Therefore, TTD analyses, excluding progressive disease as an event, is important to illustrate the influence of a treatment on HRQoL: TTD was not significantly different across any HRQoL scale or item in TTFields-treated patients except for pain and itchy skin, indicating that treatment with TTFields had an influence only on the level of pain and itchy skin. In patients treated with TTFields, TTD was significantly longer for pain (13.4 vs 12.1 months; $P < .01$) and significantly shorter for itchy skin (8.2 vs 14.4 months; $P < .001$). The difference between deterioration-free survival and TTD indicates the importance of disease progression (rather than treatment) as a key event driving HRQoL decline, as suggested by previous studies.^{26,27} Moreover, in only 1% of patients, regardless of treatment arm, was a clinically relevant improvement in HRQoL seen after initial deterioration, supporting this observation. Taken together, the results of the deterioration-free survival and TTD analyses support the results of the longitudinal analysis by showing that the addition of TTFields to the standard of care did not adversely affect HRQoL. In fact, the delay in TTD for pain seen in TTFields-treated patients may reflect a delay in the occurrence of tumor-related headaches (although not significant, patients in the TTFields plus temozolomide arm had a longer TTD compared with patients in the temozolomide-alone arm for headaches: hazard ratio, 0.77; 95% CI, 0.54-1.10; $P = .16$). Future studies are needed to better understand this finding, as the median TTD values for pain were longer than the median progression-free survival for both arms.

Limitations

A common problem in many cancer clinical trials, as in this study, is missing HRQoL data. This absence is especially apparent during the follow-up period, hampering longitudinal data analysis. Patients with better prognostic factors and a good treatment response will be overrepresented at later stages.^{28,29} However, our mixed-model analyses, accounting for missing data, confirmed the results found in the mean change from baseline analyses. Another limitation of clinical trials is generalizability of results—patients in clinical trials may not be representative of a general glioblastoma population. Patients in this trial were included only if they successfully completed the combined radiochemotherapy. In addition, it may be that not all patients are prepared to accept wearing the TTFields device. Nevertheless, patients participating in this trial were similar with respect to clinical characteristics to those participating in the EORTC 26981 study¹² comparing radiotherapy alone with radiotherapy plus temozolomide. Lastly, many factors may affect HRQoL, such as age, comorbidity, tumor characteristics, previous antitumor treatment (eg, radiation dose), and supportive treatment. However, it is unlikely that these factors influenced our conclusion, as the objective of this study was to compare HRQoL results between 2 treatment arms in which patients were similar due to randomization.

Conclusions

Use of TTFields prolongs progression-free and overall survival in patients with glioblastoma. The addition of this novel device-delivered treatment neither negatively affects nor improves functioning and well-being of the patient, including critical HRQoL issues, such as role, social, and physical functioning. Patients reported more itchy skin, which is a direct and expected consequence of the placement of transducer arrays on the patients' scalp. Considering the net clinical benefit, our HRQoL data support the addition of TTFields to standard therapy in patients with glioblastoma.

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Conflict of Interest Disclosures: Dr Taphoorn has performed paid consultancy for Hoffmann-La Roche. Dr Lavy-Shahaf is an employee of and received personal fees from Novocure during the conduct of the study. Drs Weinberg and Kirson are employees of and own minority stock in Novocure. Dr Taillibert received fees from Centre-de-Recherche-en-Neuro-Oncologie for enrolling patients at Salpêtrière University Hospital during the conduct of the study. Dr Idhah received research support from Foundation ARC, IntselChimos, Beta-Innov, and Carthera and travel support from Carthera and Hoffmann-La Roche and served as a paid member of the advisory boards of BMS, Hoffmann-La Roche, and Lettre du Cancérologue. Dr Hottinger received research support from Novocure and served on advisory boards of Servier and BMS (fees paid to the institution). Dr Roth served as a paid member of the advisory boards of Roche and MSD and received personal fees for lectures on behalf of BMS and Novocure. Dr Ram received grants and personal fees from and owns minority stock in Novocure. Dr Stupp received nonfinancial support from Novocure, and his institution received fees from Celgene, Novartis, AbbVie, Merck KGaA (Darmstadt), and MSD-Merck & Co. Dr Stupp's spouse is a full-time employee of Celgene. No other conflicts were reported.

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Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

A Randomized Clinical Trial

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IMPORTANCE Tumor-treating fields (TTFields) is an antimitotic treatment modality that interferes with glioblastoma cell division and organelle assembly by delivering low-intensity alternating electric fields to the tumor.

OBJECTIVE To investigate whether TTFields improves progression-free and overall survival of patients with glioblastoma, a fatal disease that commonly recurs at the initial tumor site or in the central nervous system.

DESIGN, SETTING, AND PARTICIPANTS In this randomized, open-label trial, 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) were enrolled at 83 centers (July 2009-2014) and followed up through December 2016. A preliminary report from this trial was published in 2015; this report describes the final analysis.

INTERVENTIONS Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy (n = 466) or temozolomide alone (n = 229). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered (≥ 18 hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups (150-200 mg/m²) for 5 days per 28-day cycle (6-12 cycles).




MAIN OUTCOMES AND MEASURES Progression-free survival (tested at $\alpha = .046$). The secondary end point was overall survival (tested hierarchically at $\alpha = .048$). Analyses were performed for the intent-to-treat population. Adverse events were compared by group.

RESULTS Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76; $P < .001$). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide vs no patients who received temozolomide alone.

CONCLUSIONS AND RELEVANCE In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

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Glioblastoma is the most common and aggressive primary brain tumor with an annual incidence of 3.19 per 100 000.¹⁻⁵ The disease course is typically rapid, with only approximately 1 in 4 patients alive 2 years after diagnosis, and only 5% to 10% of patients alive at 5 years.^{1,6,7}

Since the current standard of care was established, consisting of surgical resection or biopsy, followed by radiotherapy with concomitant temozolomide chemotherapy, followed by maintenance temozolomide for 6 to 12 months,⁶ little progress has been made in the treatment of this disease.^{3,8,9} Most trials have shown median progression-free survival and median overall survival from diagnosis of 6.2 to 7.5 months and 14.6 to 16.7 months, respectively.^{1-6,8}

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively affects dividing glioblastoma cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the scalp.^{10,11} Tumor-treating fields cause mitotic arrest and apoptosis of rapidly dividing cells.^{10,11} Preclinical studies demonstrated increased sensitivity to chemotherapy with the addition of TTFields in human glioblastoma cell lines and in animal tumor models.¹² In a randomized phase 3 trial involving 237 patients with recurrent glioblastoma whose several lines of prior therapy had failed, TTFields monotherapy was compared with the treating physicians' best choice of salvage chemotherapy. Although no survival difference was observed, the higher objective response rate (12% vs 7%) suggested single-modality activity of TTFields.¹³

In 2009, this randomized phase 3 clinical trial was initiated, comparing maintenance temozolomide alone with maintenance temozolomide in combination with TTFields among patients with glioblastoma. A preplanned interim analysis involving the first 315 patients randomized was previously reported and demonstrated improved progression-free and overall survival.¹⁴ This article reports the final analysis involving all 695 randomized patients, with a median follow-up of 40 months and a minimum follow-up of 24 months.

Methods

The study was approved by the institutional review boards or ethics committees of all participating centers, and all patients provided written informed consent before entering the study. The trial protocol and statistical analysis plan are included in Supplement 1.

Study Population

Patients eligible for this study were aged 18 years or older, had a Karnofsky performance score of 70 or higher (a score of ≥ 70 ensures independence in activities of daily living), and had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization [WHO] grade IV astrocytoma¹⁵). All participants had undergone maximal safe debulking surgery when feasible or biopsy and had completed standard radiotherapy with concomitant temozolomide at the time of enrollment. Prior use of implanted

Key Points

Question Does the use of tumor-treating fields (TTFields), consisting of low-intensity, alternating electric fields delivered via transducer arrays applied to the scalp, when added to maintenance temozolomide chemotherapy, improve progression-free survival for patients with glioblastoma?

Findings In this randomized clinical trial involving 695 patients with glioblastoma who had completed initial radiochemotherapy, median progression-free survival from randomization was 6.7 months in the TTFields plus temozolomide group and 4.0 months in the temozolomide-alone group (hazard ratio, 0.63), a significant difference.

Meaning Among patients with glioblastoma, the addition of TTFields to maintenance temozolomide chemotherapy resulted in statistically significant improvement in survival. These results are consistent with those reported in a previous interim analysis.

carmustine wafers was allowed. Patients with evidence of progressive disease following radiochemotherapy, infratentorial tumor location, and severe comorbidities were excluded. Adequate hematological, liver, and kidney function tests to allow for temozolomide chemotherapy were required.^{6,14,16}

Study Design and Treatment

This multicenter, open-label, randomized clinical phase 3 trial, recruited 695 patients at 83 sites in North America, Europe, the Republic of Korea, and Israel. The trial was designed to test the efficacy and safety of TTFields in combination with best standard of care in the treatment of newly diagnosed glioblastoma. Patients were randomized after the end of radiochemotherapy at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m²/d for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. Tumor treating fields treatment was to be initiated at least 4 weeks but not more than 7 weeks from the last day of radiotherapy. Maintenance temozolomide was delivered in 28-day cycles according to the protocol established by the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) Clinical Trials Group.⁶ Extension of the duration of maintenance temozolomide beyond 6 cycles was allowed per local practice. Randomization was performed using a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by the methylation status of the O6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter (methylated, unmethylated, unknown).

Treatment with TTFields was delivered through 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Inc). Transducer array layouts were determined using a TTFields mapping software system to optimize field intensity within the treated tumor (NovoTAL, Novocure Inc). Patients were trained by the nursing staff and device technician to operate the device independently, replace transducer arrays, and troubleshoot any

Figure 1. Recruitment and Inclusion of Patients in the Study



alarm conditions (eg, disconnected cables). All treatment was delivered on an outpatient basis and at home. The transducer arrays were supplied in individual sterile packages, and replaced by the patient, a caregiver, or a device technician twice a week. Although uninterrupted treatment was recommended, the patient could take short treatment breaks to tend to personal needs. The patient was advised to continue treatment for no fewer than 18 hours a day.

If tumor progression occurred, second-line therapy was offered per local practice. However, in the experimental group, TTFields could be continued until second radiologic progression occurred or for a maximum of 24 months.

Patient Surveillance and Follow-up

Patients diagnosed with glioblastoma who had undergone surgical resection or biopsy and had received standard radiochemotherapy were randomized to receive either TTFields plus temozolomide or temozolomide alone between July 2009 and December 2014 (Figure 1). The database was locked for final analysis on December 28, 2016. Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance

temozolomide with or without TTFields. A complete physical examination and laboratory parameters were performed within 1 week of treatment start. Evaluation also included the EORTC QLQ-C30 quality-of-life questionnaire with its brain-specific module (BN-20)^{17,18} and a Mini-Mental State Examination (a test result of 27-30 points is considered normal function). Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months.

Adverse events were recorded for 2 months after treatment discontinuation according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) v3.0. Adverse events were presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the analysis.

Independent Radiological Review

Magnetic resonance imaging was performed at 2-month intervals until second progression. In the event of clinical progression, MRI was to be performed within 1 week after the investigator had become aware of it. All MRIs were reviewed by 2 blinded central independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression (Macdonald criteria¹⁹). For cases

in which the 2 reviewers were not in agreement, a third blinded radiologist adjudicated between them.

Central MGMT Testing, Pathology Review, and Molecular Analyses

In patients with paraffin-embedded tumor tissue available, evaluation of the MGMT methylation status was performed using quantitative methylation-specific polymerase chain reaction^{3,20} by a central laboratory licensed by MDxHealth. If the MGMT methylation status could not be determined centrally prior to randomization, local MGMT methylation status was used for stratification. All data analyses were based on the central blinded assessment.

Patients were included based on initial local histological diagnosis. A retrospective pathology review and evaluation of molecular testing was performed by a neuropathologist (B.L.) and molecular biologist (M.E.H.). Deletion of chromosomal arms 1p and 19q and amplification of the epidermal growth factor receptor (*EGFR*) were evaluated by fluorescent in situ hybridization (FISH), immunohistochemistry (IHC), or both; and the mutation status of the isocitrate dehydrogenase 1 (*IDH1*) gene was determined by immunohistochemistry for the most common mutant *IDH1-R132H* as described previously.²¹ For cases in which insufficient tissue was available for *EGFR* FISH, the result of *EGFR* IHC was used as a surrogate (Hirsch score, ≥ 200 amplified; < 200 , not amplified).²²

Outcomes

Primary and Secondary End Points

The primary end point was progression-free survival, and the secondary end point was overall survival, with analyses conducted in the intent-to-treat population.

The protocol defined that overall survival would be analyzed in a per-protocol population including only patients who received their original allocated treatments. However, 26 patients (11%) in the temozolomide-alone control group crossed over and received TTFields after December 2014, following release of the results of the interim analysis of the trial. These 26 patients had more favorable baseline characteristics than the rest of the control patients (MGMT methylated, 48%; Karnofsky performance score, 80-100; time from end of radiotherapy to randomization, 31 days) and received more cycles of temozolomide (median, 10.5 cycles). To avoid possible bias, these patients were analyzed as randomized in the control group according to the intent-to-treat principle.

Exploratory End Points

Other predefined exploratory end points were percentage of patients alive and progression free at 6 months, annualized survival rates, quality of life, Mini-Mental State Examination, and Karnofsky performance score. The quality-of-life data are not reported in this article.

Statistical Analysis

Primary and Secondary End Points

For the primary end point of progression-free survival, the calculated sample size was 700 patients aimed to detect a hazard ratio (HR) of 0.78 or less, with 80% power allowing for 10%

loss to follow-up and a 2-sided $\alpha = .05$. Overall survival was a powered secondary end point in the study (80% power; HR, 0.76; 2-sided $\alpha = .05$). To avoid multiplicity, overall survival was to be tested statistically only if the primary end point of the study was met.

To allow for 2 analyses in the trial, the final type I error of 0.05 was split between the interim and final analyses based on a standard α spending function (Lan and DeMets^{23,24}). The primary end point at the final analysis would be achieved if progression-free survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test (stratified by the randomization strata) with an α of .046 (an α of 0.014 was spent on the interim analysis).

The secondary end point would be achieved at the final analysis if overall survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an α of .048 (an α of .006 was spent on the interim analysis).

Missing Data

For the analysis of progression-free survival patients were censored for progression when treatment was changed before evidence of progression (at the date of treatment change), at the date of their last MRI if lost to follow up, or upon reaching the cutoff date without progression. For the analysis of overall survival, patients without a known date of death were censored at the last known date they were documented to be alive.

Exploratory End Points

The exploratory end points of annual survival rates and the rate of progression-free survival at 6 months were compared between groups using a 1-sided Z distribution of the Kaplan-Meier estimates of the survival rates at the defined time point. In addition, the Cox proportional hazards model was used to analyze both progression-free survival and overall survival controlling for treatment group, age, sex, MGMT methylation status (as determined by the central laboratory), tumor location in the brain, and country of residence (United States vs all other countries). The threshold for significant interactions in the model was specified at an α of .05.

Post Hoc Analysis

Post hoc analyses of prespecified subgroups (MGMT promoter methylation status, extent of resection (complete, partial resection, or biopsy), age (continuous), performance status (90-100 vs ≤ 80), sex, and geographic region (United States vs the rest of the world) was performed using a multivariate analysis testing the difference between treatment groups while controlling for the other prognostic factors.

Analysis of Adverse Events and Tolerability

Differences in the incidence of adverse events between groups was tested using a χ^2 test at an α of .05. The incidence of adverse events was also compared between groups after normalizing the incidence to the average treatment duration per group. Differences in the time to decline in Karnofsky performance score and Mini-Mental State Examination were tested using a log-rank test at an α of .05. All analyses were performed using SAS version 9.4.

Table 1. Patient and Treatment Characteristics

Characteristics	No. (%) of Patients TTFields + Temozolomide (n = 466)	No. (%) of Patients Temozolomide Alone (n = 229)
Age, y		
Median (range)	56.0 (19-83)	57.0 (19-80)
≥65	89 (19)	45 (20)
<65	377 (81)	184 (80)
Karnofsky performance score ^a		
Median (range)	90.0 (60-100)	90.0 (70-100)
90-100	308 (66)	149 (65)
≤80	154 (33)	74 (32)
Missing	4 (1)	6 (3)
Sex		
Men	316 (68)	157 (69)
Women	150 (32)	72 (31)
Region		
United States	221 (47)	118 (52)
Outside the United States	245 (53)	111 (48)
Race/ethnicity		
White	416 (89)	201 (88)
African American	3 (1)	1 (<1)
Asian	27 (6)	19 (8)
Hispanic	18 (4)	7 (3)
American Indian	1 (<1)	1 (<1)
Antiepileptic drug use at baseline	205 (44)	95 (41)
Corticosteroid use at baseline	135 (29)	64 (28)
Mini-Mental State Examination score ^b		
27-30	356 (76)	160 (70)
≤26	88 (19)	48 (21)
Missing	22 (5)	21 (9)
Extent of resection		
Biopsy	60 (13)	29 (13)
Partial resection	157 (34)	77 (33)
Gross total resection	249 (53)	123 (54)
MGMT promotor region methylation status		
Tissue available and tested	386 (83)	185 (81)
Methylated	137 (36)	77 (42)
Unmethylated	209 (54)	95 (51)
Invalid	40 (10)	13 (7)
Slides available for central pathology review	296 (64)	138 (60)
Confirmed glioblastoma	285 (96)	134 (97)
WHO grade II or III glioma	4 (1)	2 (1)
Insufficient quality for diagnosis	7 (2)	2 (1)
IDH1-R132H status		
Tissue available and tested	260 (56)	119 (52)
Mutated	19 (7)	6 (5)
Negative test results	240 (92)	113 (95)
Invalid	1 (<1)	
EGFR status		
Tissue available and tested	252 (54)	112 (49)
Amplified	102 (41)	43 (38)
Not amplified	147 (58)	68 (61)
Invalid	3 (1)	1 (1)
Tumor tissue chromosomes 1p and 19q		
Tissue available and tested	259 (56)	112 (49)
Codeletion	2 (1)	
Loss 1p only	4 (2)	1 (1)
Loss 19q only	3 (1)	3 (3)
Retained	239 (92)	102 (91)
Invalid	11 (4)	6 (5)

(continued)

Table 1. Patient and Treatment Characteristics (continued)

Characteristics	No. (%) of Patients TTFields + Temozolomide (n = 466)	No. (%) of Patients Temozolomide Alone (n = 229)
Tumor position ^c		
Corpus callosum	25 (5)	12 (5)
Frontal lobe	190 (41)	84 (37)
Occipital lobe	58 (12)	27 (12)
Parietal lobe	146 (31)	89 (39)
Temporal lobe	191 (41)	90 (40)
Missing	3 (1)	3 (1)
Tumor location ^c		
Left hemisphere	214 (46)	99 (43)
Right hemisphere	249 (53)	127 (55)
Both hemispheres	4 (1)	2 (1)
Corpus callosum	15 (3)	9 (4)
Missing	1 (<1)	1 (<1)
Treatment delivery		
Completed standard radiation therapy		
57-63 Gy	422 (91)	212 (93)
<57 Gy	21 (5)	11 (5)
>63 Gy	18 (4)	3 (1)
Dose not reported	5 (1)	3 (1)
Concomitant radiation therapy and temozolomide		
Yes	433 (93)	212 (93)
No record available	33 (7)	17 (7)
Time from last day of radiation treatment to randomization, median (range), d	37 (15-128)	36 (15-70)
Time from initial diagnosis to randomization, median (range), mo	3.8 (1.7-6.2)	3.7 (1.4-6.3)
Temozolomide cycles, median (range)	6 (0-51)	5 (0-33)
Tumor-treating fields therapy		
Duration, median (range), mo	8.2 (0-82)	
≥18 h/d (first 3 mo of treatment), mean	347 (75)	

Abbreviations: EGFR, epidermal growth factor receptor gene; IDH1-R132H, isocitrate dehydrogenase 1 (IDH1) R132H mutation site; MGMT, O⁶-methylguanine-DNA-methyltransferase gene; TTFields, tumor-treating fields; WHO, World Health Organization.

^a Karnofsky performance score ranges from 0 to 100 in 10-point increments, with a higher score representing better performance status.

^b Scores range from 1 to 30, with a higher score representing better cognitive function.

^c Multiple positions for each patient allowed (for multifocal tumors).

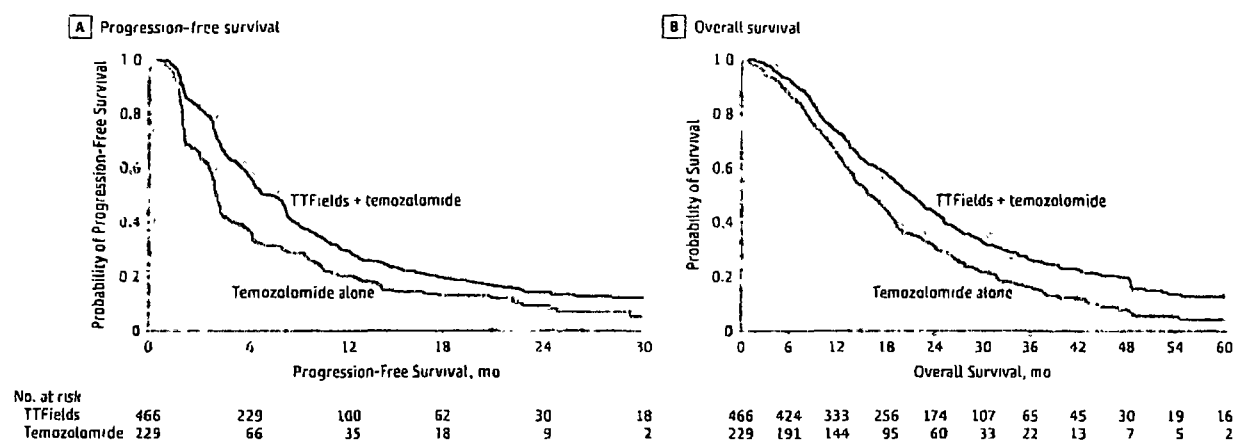
Results

Study Participants

Four hundred and sixty-six patients were randomized to receive TTFields plus temozolomide and 229 to receive temozolomide alone (Figure 1). Patient baseline characteristics were balanced between the 2 groups (Table 1). The median age was 56 years (interquartile range [IQR], 48-63 years), 68% were men, and median Karnofsky performance score was 90%. Eighty-nine percent of patients were white, and 49% of the patients were treated in the United States.

Fifty-four percent had undergone a gross total resection (>95% of the tumor removed; as assessed and reported by the surgeon), 13% of patients had a diagnostic biopsy only. Histological slides for central pathology review were available for

Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



A, Median progression-free survival from randomization for the tumor-treating fields (TTFields) plus temozolomide group was 6.7 months and was 4.0 months for the temozolomide-alone group (hazard ratio [HR], 0.63; 95% CI, 0.52-0.76; $P < .001$). B, Median survival from randomization was 20.9 months for the TTFields plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Median follow-up was 44 months (range, 25-91 months) in both groups.

434 of 695 patients (62%). The local diagnosis of glioblastoma was confirmed in 419 of 434 patients (97%). For 6 cases WHO grade II or III diagnoses were made, and for the remaining 9 patients, the available tissue for review did not allow for a definitive diagnosis or showed no tumor, yet all these patients were included in the intent-to-treat analysis. Tumor tissue for *MGMT* testing was available for 82% of the patients; of the cases with a valid test (518 of 571) 41% were *MGMT* methylated (40% TTFields plus temozolomide group and 45% for the temozolomide-only group). In 7% of tumors, expression of the *IDH1*-R132H mutant was demonstrated by a positive immunohistochemistry, *EGFR* was amplified in 40%.

Tumor location (lobe, hemisphere) in the brain was also comparable between the groups. The median time from histological diagnosis to randomization was 3.8 months (range, 1.7-6.2 months) for patients in the TTFields plus temozolomide group, and 3.7 months (range, 1.4-6.3 months) for those in the temozolomide-only group. Median time from the end of radiotherapy to randomization was 37 days in the TTFields plus temozolomide group and 36 days in the temozolomide-only group and occurred in most patients after starting of the first cycle of maintenance temozolomide. Median time from randomization to TTFields was 5 days (IQR, 3-7 days).

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until first tumor progression was 6 (range, 0-51) for the TTFields plus temozolomide group and 5 (range, 0-33) for the temozolomide-only group; the median duration of TTFields treatment was 8.2 months (range, 0-82 months), 51% ($n = 237$) of patients continued TTFields after the first progression.

Efficacy End points

After a median follow-up of 40 months (IQR, 34-66 months), and a minimum follow-up of 24 months, the primary end point

of median progression-free survival was 6.7 months (95% CI, 6.1-8.1 months) for patients treated with TTFields plus temozolomide vs 4.0 months (95% CI, 3.8-4.4 months) for patients treated with temozolomide alone, for a proportional hazard ratio (HR) of 0.63 (95% CI, 0.52-0.76; $P < .001$; stratified log-rank test; Figure 2A). For the secondary end point of overall survival, the median survival duration from randomization was 20.9 months (95% CI, 19.3-22.7 months) in the TTFields plus temozolomide group vs 16.0 months (95% CI, 14.0-18.4 months) in the temozolomide-only group, proportional HR of 0.63 (95% CI, 0.53-0.76; $P < .001$; stratified log-rank test; Figure 2B).

In exploratory analyses, the percentage of patients alive at 2 years from randomization was 43% (95% CI, 39%-48%); at 3 years, 26% (95% CI, 22%-31%), and at 5 years, 13% (95% CI, 9%-18%) in the TTFields plus temozolomide group and for the temozolomide-only group at 2 years was 31% (95% CI, 25%-38%; $P < .001$); at 3 years, 16% (95% CI, 12%-23%; $P = .009$); and at 5 years, 5% (95% CI, 2%-11%; $P = .004$). Progression-free survival at 6 months was 56% (95% CI, 51%-61%) for patients treated with TTFields plus temozolomide and 37% (95% CI, 30%-44%) with temozolomide only ($P < .001$) (Table 2).

An exploratory Cox proportional hazards model adjusting for Karnofsky performance score, *MGMT* promoter methylation status, geographic region, age, tumor location, and extent of resection were consistent with the findings of the progression-free and overall survival analyses. The following factors were associated with longer overall survival: TTFields plus temozolomide treatment (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$), female sex (HR, 0.76, 95% CI, 0.63-0.92; $P = .005$), methylated *MGMT* promoter (HR, 0.50; 95% CI, 0.41-0.62; $P < .001$), younger age (as a continuous variable; HR, 0.978 per year; 95% CI, 0.969-0.985; $P < .001$) and higher Karnofsky performance score (as a categorical variable in 10 point increments; $P < .001$). Patients with frontal tumors had non-significantly longer survival (HR = 0.82, CI 0.67-1.01, $P = .061$). Country of treatment and extent of resection were not

Table 2. Summary of Study End Points^a

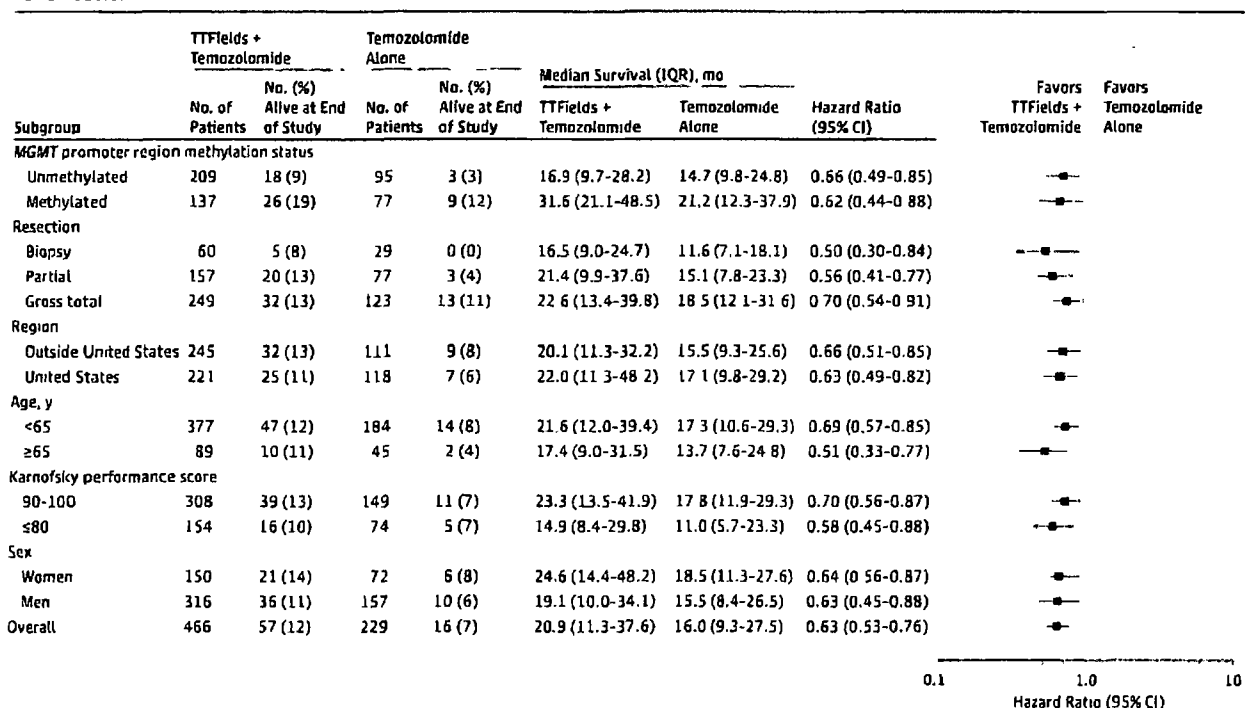
	TTFields + Temozolomide (n = 466)	Temozolomide Alone (n = 229)	Between-Group Differences
Progression-free survival			
Primary end point, median (95% CI), mo	6.7 (6.1-8.1)	4.0 (3.8-4.4)	2.7 (2.1-4.2)
Overall survival			
Secondary end point, median (95% CI), mo	20.9 (19.3-22.7)	16.0 (14.0-18.4)	4.9 (2.3-7.9)
Exploratory end points, % (95% CI)			
Progression-free 6-mo survival rate	56 (51-61)	37 (30-44)	19 (15-23)
Annual survival rates, y			
1	73 (69-77)	65 (59-72)	18 (10-25)
2	43 (39-48)	31 (25-38)	12 (4-18)
3	26 (22-31)	16 (12-23)	10 (3-17)
4	20 (16-25)	8 (4-14)	12 (5-19)
5	13 (9-18)	5 (2-11)	8 (2-14)

Abbreviation:

TTFields, tumor-treating fields.

^a Survival rates are actuarial estimates according to the Kaplan-Meier method.

Figure 3. Overall Survival for Each Prognostic Patient Subgroup of Patients Treated With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone



Data points represent Cox hazard ratios of overall survival in each subgroup of patients treated with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone and were adjusted for the other subgroups. Error bars represent 95% CIs of the hazard ratios. The Karnofsky performance score is measured from 0 to 100 in 10-point increments, with higher scores indicating better the patient performance status.

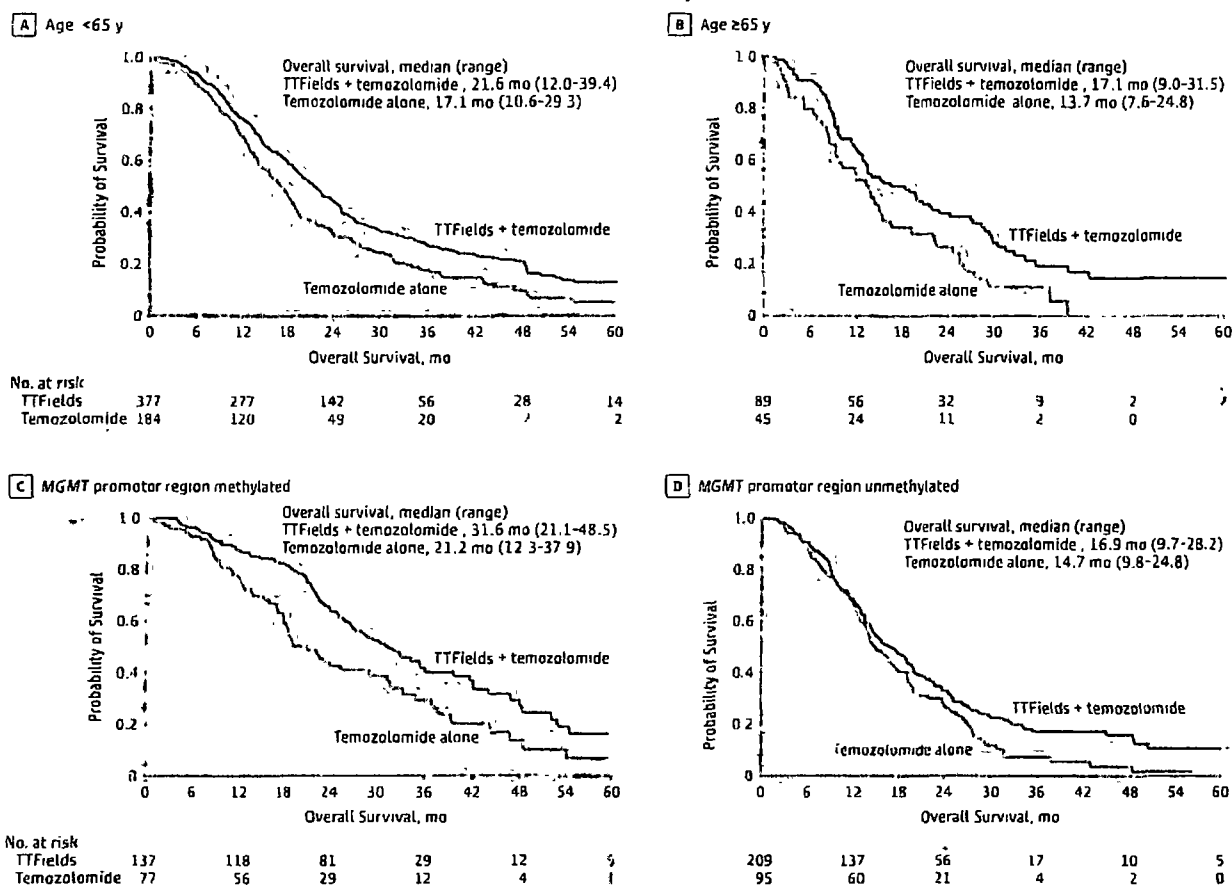
IQR, indicates interquartile range; MGMT, O⁶-methylguanine-DNA methyltransferase promoter region methylation status.

associated with a significant difference in survival ($P = .101$ and $P = .183$, respectively).

Post Hoc Subgroup Analysis

In post hoc analyses, TTFields plus temozolomide was associated with an increase in progression-free survival and overall survival (Figure 3; Cox proportional hazards, $P < .05$ for the treatment effect within each subgroup) in all subgroups of

patients regardless of age, sex, Karnofsky performance score, MGMT promoter methylation status, geographic region, or extent of resection. Patients 65 years or older had shorter survival than patients younger than 65 years. In both age groups, TTFields plus temozolomide was associated with significantly increased survival compared with temozolomide alone for older (HR, 0.51; 95% CI, 0.33-0.77) and younger patients (HR, 0.67; 95% CI, 0.55-0.82; Figure 4A and Figure 4B).

Figure 4. Overall Survival by Patient Age and by *MGMT* Promotor Region Methylation Status

A, In comparing tumor-treating fields (TTFields) plus temozolomide vs temozolomide alone among patients younger than 65 years the hazard ratio (HR) was 0.67 (95% CI, 0.55-0.82). B, In comparing the 2 treatments among patients 65 years or older, the HR was 0.51 (95% CI, 0.22-0.77). C, In comparing the treatments among patients with *O*⁶-methylguanine-DNA methyltransferase

MGMT promotor region methylation, the HR was 0.62 (95% CI, 0.43-0.88). D, In comparing the treatments among patients without the *MGMT* promotor region methylation, the HR was 0.66 (95% CI, 0.49-0.85). The median follow-up of patients was 44 months (range, 25-91 months) in all groups.

Patients with tumors that lacked *MGMT* promoter methylation had a significantly shorter survival than patients with tumors with *MGMT* promoter methylation, although use of TTFields with temozolomide was associated with longer survival (HR, 0.66; 95% CI, 0.49-0.85 both in patients with tumors that were *MGMT* methylated and tumors that were unmethylated, respectively; Figure 4C and Figure 4D). In the TTFields plus temozolomide group, 265 patients who were treated with TTFields for 18 hours a day or more (monthly average in the first 6 months of treatment) had longer survival than 185 patients treated less than 18 hours a day (22.6 months, 95% CI, 19.7-25.1 months vs 19.1 months, 95% CI, 16.5-21.9; HR, 0.65; 95% CI, 0.49-0.85; $P = .009$).

Adverse Events and Tolerability

The addition of TTFields to temozolomide therapy was not associated with any significant increase in rates of systemic adverse events compared with temozolomide therapy alone (48% vs 44%, respectively; $P = .58$; Table 3), and the overall incidence,

distribution, and severity of adverse events were not statistically different in patients in the 2 treatment groups. The numerically higher incidence of some adverse events in the TTFields plus temozolomide group was a reflection of the longer duration of temozolomide treatment in this group due to delayed occurrence of progression. When adverse event incidence normalized to duration of treatment was analyzed, these differences disappeared. The only exception was a higher incidence of localized skin toxic effects (medical device site reaction beneath the transducer arrays) in patients treated with TTFields plus temozolomide; mild to moderate skin irritation was observed in 52% of patients, and severe (grade 3) skin involvement occurred in 2%. Anxiety, confusion, insomnia, and headaches which were reported more frequently (statistically nonsignificant) in patients treated with TTFields at the interim analysis were not seen in the final adverse event analysis of the trial. The incidence of seizures was identical in the 2 groups.

To estimate tolerability, prespecified exploratory analyses of the association of TTFields device use with patients'

Table 3. Adverse Events by Body System and Severity ($\geq 5\%$ Incidence in Any Group)

	Grade 3-4 Events, No. (%) of Patients	
	TTFields + Temozolomide (n = 456)	Temozolomide Alone (n = 229)
≥ 1 Adverse event	218 (48)	94 (44)
Blood and lymphatic system disorders ^a	59 (13)	23 (11)
Thrombocytopenia	39 (9)	11 (5)
Gastrointestinal disorders	23 (5)	8 (4)
Asthenia, fatigue, and gait disturbance	42 (9)	13 (6)
Infections	32 (7)	10 (5)
Injury, poisoning, and procedural complications (falls and medical device site reaction)	24 (5)	7 (3)
Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia)	16 (4)	10 (5)
Musculoskeletal and connective tissue disorders	21 (5)	9 (4)
Nervous system disorders	109 (24)	43 (20)
Seizures	26 (6)	13 (6)
Respiratory, thoracic and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia)	24 (5)	11 (5)

Abbreviation:

TTFields, tumor-treating fields.

^a The numerically slightly higher incidence of hematological toxicity, fatigue, and some other adverse effects are due to the longer treatment duration and observation time in the experimental group. The differences disappear when data are normalized to treatment duration.

activities of daily life and cognition were performed using the Karnofsky performance score and the Mini-Mental State Examination. Time to a sustained 6-point decline in the Mini-Mental State Examination score was significantly longer in the TTFields plus temozolomide group than the temozolomide-alone group (16.7 months; 95% CI, 14.7-19.0 months vs 14.2 months; 95% CI, 12.7-17.0 months, respectively; HR, 0.79; 95% CI, 0.66-0.95; $P = .01$). Time to a sustained 10-point decrease in Karnofsky performance score was also significantly longer in the TTFields plus temozolomide group than in the temozolomide-alone group (5.5 months; 95% CI, 5.0-6.3 months vs 3.9 months; 95% CI, 3.1-5.2 months, respectively; HR, 0.80; 95% CI, 0.67-0.95; $P = .009$).

Discussion

In the final analysis of this randomized phase 3 trial, the addition of the TTFields treatment to standard temozolomide maintenance therapy, compared with standard temozolomide maintenance therapy alone, resulted in increased progression-free survival and overall survival in patients with newly diagnosed glioblastoma. After a median follow-up of 40 months, the addition of TTFields to temozolomide, compared with temozolomide alone, resulted in longer median progression-free survival from the time of randomization, 6.7 months vs 4.0 months and longer median overall survival from randomization, 20.9 months vs 16.0 months, respectively. These findings are consistent with the preliminary results reported based on a planned interim analysis of the first 315 patients enrolled, after a median follow-up of 38 months, in which median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group (210 patients analyzed) and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide-alone group (105 patients analyzed).

In the current study, exploratory end points were consistent with the primary and secondary end points in this trial. In a post hoc analysis the effect of TTFields was observed in all clinical and molecular subgroups, including patients older than age 65 years and patients with *MGMT* unmethylated tumors.

To assess whether the improved outcome may have been related to other factors than the TTFields therapy the data were scrutinized for possible imbalances, unexpected poor performance of the control group, or differences in supportive care administered to patients between the 2 groups. Both clinical factors and molecular tumor characteristics were well balanced and comparable between the 2 groups. *MGMT* promoter methylation, the strongest predictive factor for outcome in temozolomide-treated patients,²⁵ was more prevalent in the control group (45% vs 40% of samples with a valid result). Patients with early tumor progression occurring during the first 3 months after diagnosis were not included in this trial, and so the randomized patient population had a better prognosis, for both groups, compared with other trials that had randomized patients before radiation therapy. The reported survival times were measured from randomization, not from diagnosis, so for an estimation of the overall outcome 3.8 months should be added in both groups. The RTOG 0525/Intergroup study, which evaluated dose-dense temozolomide, also randomized patients only after completion of radiochemotherapy.⁸ Outcome of the control group in the current study and of the RTOG study were very similar, and in both studies, the median survival from randomization was 16 months.

In this trial, the rates of systemic adverse effects were not significantly different in the 2 treatment groups. The occurrence of mild to moderate skin irritation related to reaction beneath the transducer arrays of the device occurred in more than half of patients in the TTFields plus temozolomide group.

These findings are in contrast to the more than 23 randomized trials conducted over the last decade that have evaluated novel agents or intensified treatment strategies

(eg, dose-dense temozolomide, cilengitide, nimotuzumab, bevacizumab, and rindopepimut^{3,5,8,26}) for treatment of patients with newly diagnosed glioblastoma and have failed to demonstrate improved survival. Innovative treatments for glioblastoma are needed.

Limitations

This study has several limitations. First, the current trial was open-label because it was considered practically unfeasible (heat and easy measure of current associated with TTFields) and ethically unacceptable to expose patients to a sham device. Although a placebo effect may affect subjective end points like quality of life or even progression-free survival by influencing the frequency of imaging and its interpretation, in the current trial a consistent benefit was observed in progression-free survival as assessed by blinded central radiology review, as well as in the gold standard of objective outcome, overall survival. Second, delivery of TTFields therapy requires the patient to continuously carry a device on a

shaved scalp and may create burdens for patients. Nevertheless, the majority of patients were able to handle the device independently or with some help from a caregiver. The fact that 75% of patients achieved treatment adherence of 75% or more (ie, using the device for ≥ 18 hours per day) indicated good tolerability. The effects of the TTFields treatment and the need for continuous use of the device on quality of life will be reported separately.

Conclusions

In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: Stupp, Taillibert, Kanner, Read, Steinberg, Lhermitte, Toms, Idbaih, Ahluwalia, Fink, Di Meco, Lieberman, Zhu, Stragiolotto, Tran, Brem, Hottinger, Kirson, Lavy-Shahaf, Weinberg, Kim, Paek, Nicholas, Bruna, Hirte, Weller, Hegi, Ram. **Drafting of the manuscript:** Stupp, Steinberg, Hottinger, Kirson, Lavy-Shahaf, Ram. **Critical revision of the manuscript for important intellectual content:** Stupp, Taillibert, Kanner, Read, Lhermitte, Toms, Idbaih, Ahluwalia, Fink, Di Meco, Lieberman, Zhu, Stragiolotto, Tran, Brem, Hottinger, Kirson, Weinberg, Kim, Paek, Nicholas, Bruna, Hirte, Weller, Palti, Hegi, Ram. **Statistical analysis:** Steinberg, Kirson, Lavy-Shahaf. **Obtained funding:** Kirson, Palti. **Administrative, technical, or material support:** Stupp, Taillibert, Kanner, Read, Toms, Di Meco, Tran, Weinberg, Kim, Paek, Nicholas, Bruna, Weller, Palti. **Supervision:** Stupp, Ahluwalia, Di Meco, Brem, Kirson, Paek, Bruna, Weller, Ram.

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Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial

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IMPORTANCE Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Most patients die within 1 to 2 years of diagnosis. Tumor-treating fields (TTFields) are a locoregionally delivered antimitotic treatment that interferes with cell division and organelle assembly.

OBJECTIVE To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229) (median time from diagnosis to randomization, 3.8 months in both groups). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis.

INTERVENTIONS Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m²/d) was given for 5 days of each 28-day cycle.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival in the intent-to-treat population (significance threshold of .01) with overall survival in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). This prespecified interim analysis was to be conducted on the first 315 patients after at least 18 months of follow-up.

RESULTS The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). Median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004).

CONCLUSIONS AND RELEVANCE In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

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Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Gy) with concomitant daily temozolomide chemotherapy, and then maintenance treatment with temozolomide for 6 to 12 months.¹ However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials.¹⁻⁴ The reported 2- and 5-year survival rates⁵ are 27% and 10%, respectively. During the last decade, all attempts to improve the outcome for patients with glioblastoma have failed when evaluated in large randomized trials.^{2-4,6,7}

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively disrupts the division of cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the shaved scalp.⁸⁻¹⁰ In preclinical models, TTFields have been shown to cause mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis.^{8,10-12} In a randomized phase 3 trial in which TTFields were compared with chemotherapy in 237 patients with recurrent glioblastoma, the use of TTFields did not prolong progression-free survival or overall survival, but the therapy was associated with better quality of life without the typical chemotherapy-associated toxic effects.¹³

Based on preclinical data demonstrating a synergistic antitumor effect with chemotherapy and TTFields, and pilot clinical feasibility data in combination with temozolomide,⁹ we initiated this phase 3 trial. The objective was to evaluate the efficacy and safety of TTFields used in combination with maintenance temozolomide in patients with glioblastoma after initial treatment with temozolomide and radiotherapy.

Methods

Study Population

Patients eligible for this study (1) had histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma¹⁴), (2) were progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and (3) had completed standard concomitant chemoradiotherapy with temozolomide. Other eligibility criteria were (1) age of 18 years or older, (2) Karnofsky Performance Status (KPS) score of 70% or higher (the KPS score describes the general condition of a patient; a KPS score $\geq 70\%$ ensures some independence in activities of daily living), and (3) adequate bone marrow, liver, and renal function.

Prior use of implanted carmustine wafers was allowed. Patients with infratentorial tumor location and severe comorbidities were excluded. All patients provided written informed consent before entering the study; the study was approved by the institutional review boards or ethics committees of all 83 participating centers. The trial protocol appears in Supplement 1.

Study Design and Treatment

This multicenter, open-label, randomized phase 3 trial was designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. After the completion of treatment with temozolomide and radiotherapy, patients were randomized at a ratio of 2 to 1 (Figure 1) to receive standard maintenance temozolomide chemotherapy (150-200 mg/m²/d for 5 days every 28 days for 6-12 cycles according to the protocol¹ from the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group) with or without the addition of TTFields. Treatment with TTFields was to be initiated within 4 to 7 weeks from the last dose of concomitant temozolomide and radiotherapy. Randomization was performed through a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by O⁶-methylguanine-DNA methyltransferase (*MGMT*) methylation status (methylated, unmethylated, or unknown).

For patients with available paraffin-embedded tumor tissue, evaluation of *MGMT* gene promoter methylation status was performed as described previously^{7,15,16} by a central laboratory blinded to treatment group (MDxHealth). If *MGMT* methylation status could not be determined centrally prior to randomization, local *MGMT* methylation status was used for stratification.

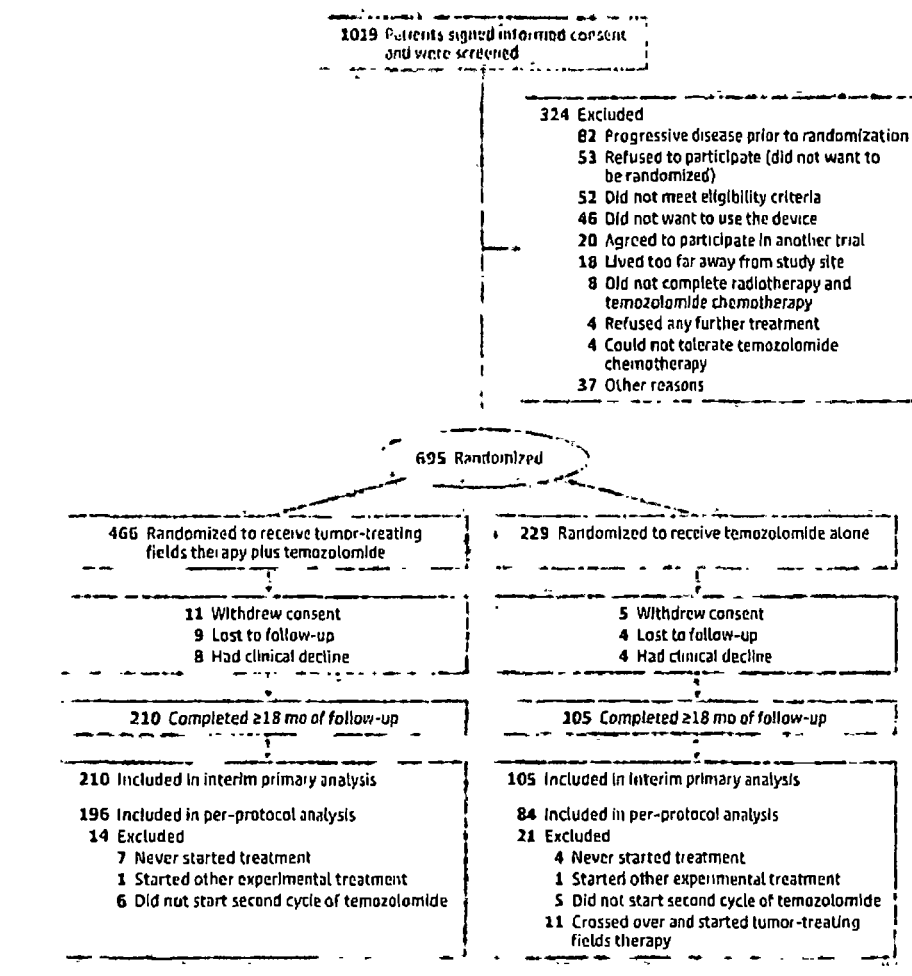
Patients in the TTFields plus temozolomide group received continuous TTFields combined with standard maintenance temozolomide. Patients receiving TTFields had 4 transducer arrays placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Ltd). Transducer array layouts were determined using a mapping software system for TTFields to optimize field intensity within the treated tumor (NovoTAL, Novocure Ltd). After being trained to operate the device, the patient continued treatment at home. The transducer arrays were supplied in sterile packaging and replaced by the patient, a caregiver, or a device technician twice per week. Although uninterrupted treatment was recommended, short treatment breaks for personal needs were allowed.

If a patient experienced tumor progression, second-line chemotherapy was offered per local practice. However, in the TTFields plus temozolomide group, TTFields could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

Patient Surveillance and Follow-up

Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance temozolomide with or without TTFields. A complete physical examination with collection of laboratory parameters was performed within 1 week of treatment initiation. The evaluation also included a quality-of-life questionnaire (QLQ-C30) that has a brain-specific module (BN-20), which was developed by the European Organisation

Figure 1. Recruitment and Inclusion of Patients in the Study



for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups.^{17,18} A Mini-Mental State Examination (a short bedside test used to evaluate cognition and memory) also was administered (a test result of 27-30 points is considered normal function).

Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months. Magnetic resonance imaging was to be performed every second month after the baseline MRI until second radiological progression in all patients. In the event of clinical progression, MRI was to be performed within 1 week after the study investigator became aware of it. All MRIs were reviewed centrally by 2 blinded independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression using the criteria developed by Macdonald et al.¹⁹ In cases in which the central reviewers were not in agreement, a third blinded radiologist adjudicated between them. The third radiologist was involved in 17% of the cases in the TTFields plus temozolomide group and in 18% of the cases in the temozolomide alone group.

The results of the central review were not communicated to the study investigator, and all treatment decisions were based on local imaging interpretation. Eight patients in the

TTFields plus temozolomide group (4%) compared with 6 patients in the temozolomide alone group (3%) were considered stable by blinded central review; however, treatment had been changed by the study investigator due to local interpretation of tumor progression. Patients were removed from the progression-free survival analysis at the date of treatment change when this occurred before evidence of tumor progression or when patients reached the cutoff date without tumor progression.

Adverse events were recorded prospectively according to the National Cancer Institute's *Common Terminology Criteria* (version 3.0) until 2 months after treatment discontinuation. Adverse events are presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the interim analysis. Treatment adherence with TTFields was recorded electronically by the device as average daily use in hours per day and information was reviewed and transferred at the monthly follow-up visit.

Statistical Considerations

The primary end point was progression-free survival in the intent-to-treat (ITT) population assessed by an independent review panel (80% power; hazard ratio [HR], 0.78; 2-sided α level

of .05). The study was also designed to have 80% power (HR, 0.76; 2-sided α level of .05) to examine overall survival as a secondary end point. To avoid an increase in the risk of a false-positive result, overall survival was to be tested statistically only if the primary end point was met.

This prespecified interim analysis was to be performed after the first 315 randomized patients reached a minimum 18-month follow-up. The final type I error rate of 0.05 was split between the interim and final analyses based on a standard spending function.²⁰⁻²² The protocol prespecified that overall survival would be analyzed in an as-treated population, excluding all patients in both treatment groups who (1) never started maintenance temozolomide, (2) had major protocol violations, (3) crossed over to the other treatment group, or (4) received TTFields outside the protocol setting.

The primary end point would be achieved in the interim analysis if progression-free survival in the ITT population was significantly longer in the intervention group compared with the control group using a stratified log-rank test with an α level of .01. The secondary end point would be achieved in the interim analysis if overall survival in the as-treated population (per-protocol population) was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an α level of .006. The confidence intervals that go with the HRs are presented as 1 minus the prespecified α level for each analysis. For example, the α level in the per-protocol interim analysis for overall survival was .006. Therefore, the corresponding confidence interval used for presenting the HRs was 1.000 – 0.006 (99.4% confidence interval). An upper confidence limit of less than 1 indicates the prespecified statistical threshold was met. An independent data and safety monitoring committee was chartered to stop the trial if the interim analysis of progression-free survival (ITT population) and overall survival (per-protocol population) surpassed these predetermined thresholds, as well as for futility or safety concerns.

In addition to these prespecified analyses, an analysis of overall survival in the ITT population was performed. Furthermore, a robustness analysis including all 695 patients enrolled in the trial served to validate the findings of the interim analysis (database lock: December 29, 2014; eAppendix 1 in Supplement 2).

Multiple imputation analyses also were performed for the trial's primary end point of progression-free survival in the ITT population to test the sensitivity of the results to possible bias using informative and interval censoring. These analyses included (1) treating all patients with informative censoring as treatment failures in the TTFields plus temozolomide group, (2) censoring all patients with informative censoring in the temozolomide alone group (worst case scenario), and (3) treating all events in the TTFields plus temozolomide group and in the temozolomide alone group as occurring differentially at different periods during the inter-MRI interval before the date of tumor progression.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.1.1.⁴³ The final analysis will be performed when all 695 patients enrolled in the study have at least 18 months of follow-up and will include prespeci-

fied subgroup analyses and additional secondary end points, including quality of life.

Results

Study Participants

Between July 2009 and November 2014, there were 695 patients with newly diagnosed glioblastoma randomized to receive either TTFields plus temozolomide ($n = 466$) or temozolomide alone ($n = 229$). Data for the interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 to temozolomide alone (Figure 1; database lock: September 5, 2014). The independent data and safety monitoring committee met in October 2014 to review the interim analysis; the trial met the predefined boundaries for success (improvement of both progression-free and overall survival) and the committee recommended study termination, thus allowing patients in the control group to crossover and receive TTFields.

After approval of study termination by the US Food and Drug Administration, the trial was closed to recruitment on November 29, 2014, after 695 patients of the planned 700 patients had already been randomized. All patients in the control group with ongoing maintenance therapy were offered to receive TTFields. At the time of this report, 35 patients in the control group crossed over to receive TTFields. Follow-up for all patients continues according to the protocol.

Patient baseline characteristics were well balanced between the 2 groups (Table 1). The median age was 57 years and 66% were male. The median KPS score was 90%. Sixty-four percent of patients had a gross total resection and 11% had only a diagnostic biopsy. Tumor tissue for central MGMT testing was available for 72% of the patients; the MGMT methylation frequency was 39% (75/191 valid tests; 39% for the TTFields plus temozolomide group and 41% for the temozolomide alone group). Tumor location in the brain was also comparable.

Carmustine wafers (Gliadel) were used at initial surgery in 2.4% of patients in the TTFields plus temozolomide group vs 2.9% of patients in the temozolomide alone group. Ninety-five percent of the patients were white and 61% were treated in the United States. The rest of the patients were treated at centers in Canada, Europe, Israel, and South Korea. The median time from diagnosis to randomization was 3.8 months (range, 2.0-5.7 months) for patients in the TTFields plus temozolomide group and 3.8 months (range, 1.4-5.7 months) for those in the temozolomide alone group. The median time from the end of treatment with temozolomide and radiotherapy to randomization was 36 days in the TTFields plus temozolomide group and 38 days in the temozolomide alone group; 53% of patients were randomized after having started the first cycle of maintenance temozolomide. The median time from randomization to initiation of TTFields was 5 days.

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the TTFields

Table 1. Patient Baseline Characteristics and Treatment Details

	All Patients (N = 315)	TTFields Plus Temozolomide (n = 210)	Temozolomide Alone (n = 105)
Age, y			
Mean (SD)	55.8 (11.1)	55.3 (11.3)	56.8 (10.5)
Median (range)	57 (20-83)	57 (20-83)	58 (21-80)
Karnofsky Performance Status score, median (range), % ^a	90 (60-100)	90 (60-100)	90 (70-100)
Sex, No. (%)			
Male	207 (66)	140 (67)	67 (64)
Female	108 (34)	70 (33)	38 (36)
Use at baseline, No. (%)			
Antiepileptic medication	126 (40)	88 (42)	38 (36)
Corticosteroid therapy	77 (24)	51 (24)	26 (25)
Mini-Mental State Examination score, No. (%) ^b			
≤26	45 (15)	31 (15)	14 (13)
27-30	247 (78)	174 (83)	73 (70)
Unknown	23 (7)	5 (2)	18 (17)
Extent of resection, No. (%)			
Biopsy	34 (11)	23 (11)	11 (10)
Partial resection	79 (25)	52 (25)	27 (26)
Gross total resection	202 (64)	135 (64)	67 (64)
Tissue available and tested, No. (%)			
MGMT methylation	75 (33)	49 (32)	26 (35)
No methylation	116 (51)	79 (52)	38 (51)
Invalid test result	36 (16)	24 (16)	11 (15)
Region, No. (%)			
United States	191 (61)	127 (60)	64 (61)
Rest of world	124 (39)	83 (40)	41 (39)
Completed radiation therapy, No. (%)			
<57 Gy	18 (6)	13 (6)	5 (5)
60 Gy (standard; ±5%)	291 (92)	191 (91)	100 (95)
>63 Gy	6 (2)	6 (3)	0 (0)
Concomitant temozolomide use, No. (%)			
Yes	308 (98)	207 (99)	101 (96)
Unknown	7 (2)	3 (1)	4 (4)
Time from event to randomization, median (range), d			
Last day of radiotherapy	37 (13-68)	36 (13-53)	38 (13-68)
Initial diagnosis	114 (43-171)	115 (59-171)	113 (43-170)
No. of maintenance temozolomide cycles until first tumor progression, median (range)	6 (1-26)	6 (1-26)	4 (1-24)
Duration of treatment with TTFields, median (range), mo	9 (1-58)	9 (1-58)	
Adherence to TTFields therapy ≥75% during first 3 mo of treatment		157 (75)	

Abbreviations: MGMT, O⁶-methylguanine-DNA methyltransferase; TTFields, tumor-treating fields.

^a A higher score indicates better functional status.

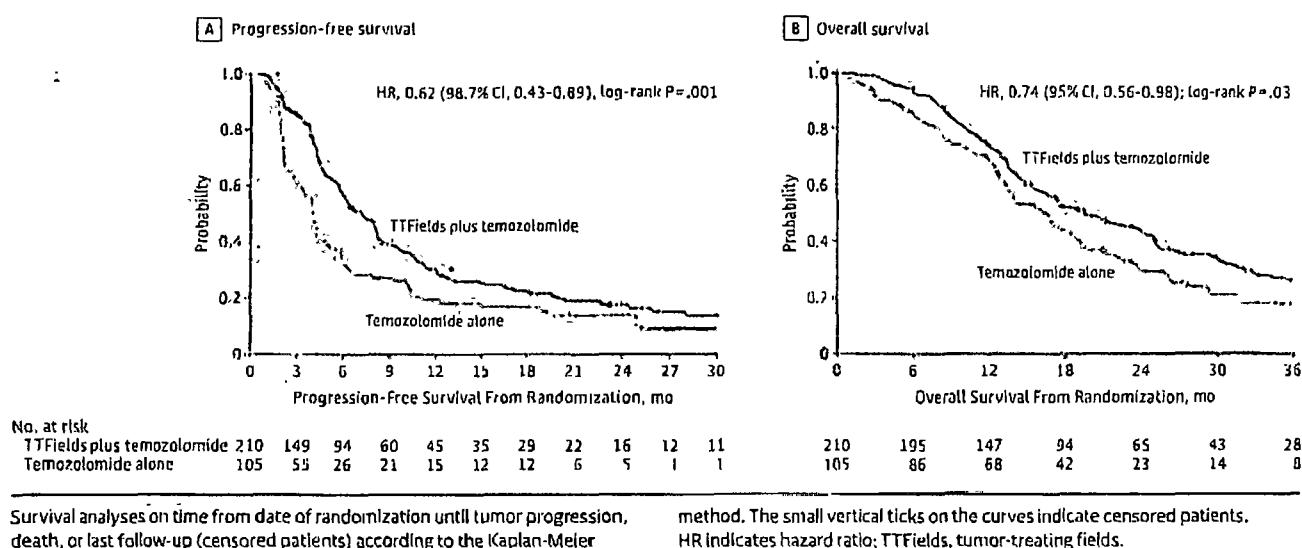
^b A higher score indicates better cognitive capability.

plus temozolomide group and 4.0 cycles (range, 1-24 cycles) for patients in the temozolomide alone group; the median duration of treatment with TTFields was 9 months (range, 1-58 months). Two-thirds (n = 141) of patients in the TTFields plus temozolomide group continued treatment with TTFields after first tumor progression. Three-quarters (n = 157) of patients receiving treatment with TTFields were adherent to therapy (ie, wearing the device >18 hours per day on average during the first 3 treatment months).

Efficacy End Points

As prespecified, the primary end point for the efficacy results was based on progression-free survival in the ITT population of the interim analysis data set. After a median follow-up of 38 months (range, 18-60 months), the median progression-free survival from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group compared with 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (HR, 0.62 [98.7% CI, 0.43-0.89];

Figure 2. Survival Curves for Patients Included in the Interim Analysis in the Intent-to-Treat Population



stratified log-rank $P = .001$; Figure 2A). Thus, adding TTFIELDS to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

As per the statistical analysis plan, overall survival was to be tested in a prespecified per-protocol population only after the primary end point was found to surpass the threshold for significance in the interim analysis. Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFIELDS plus temozolomide group ($n = 196$) compared with 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group ($n = 84$) (HR, 0.64 [99.4% CI, 0.42-0.98]; stratified log-rank $P = .004$). The details on the per-protocol population and analyses are summarized in eAppendix 2 in Supplement 2.

In additional analyses in the ITT population, the median overall survival was 19.6 months (95% CI, 16.6-24.4 months) in the TTFIELDS plus temozolomide group compared with 16.6 months (95% CI, 13.6-19.2 months) in the temozolomide alone group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank $P = .03$; Figure 2B). The percentage of patients alive at 2 years following enrollment was 43% in the TTFIELDS plus temozolomide group and 29% in the temozolomide alone group ($P = .006$).

To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Patient characteristics of all patients randomized did not differ significantly from the interim data set, and the results for the main end points were similar in these analyses compared with the interim analysis (eAppendix 1 in Supplement 2).

Second-line treatments, such as nitrosoureas, temozolomide rechallenge, and bevacizumab, were received by 67% of the patients in the TTFIELDS plus temozolomide group compared with 57% in the temozolomide alone group; about 40% of second-line therapies included bevacizumab and about 40% included nitrosoureas. The type of chemotherapy used at recurrence was balanced between treatment groups.

Secondary imputation analyses of progression-free survival with relation to the effects of interval and informational censoring did not change the conclusions of the primary progression-free survival analysis (eAppendix 3 in Supplement 2).

Safety and Tolerability

The addition of TTFIELDS to temozolomide therapy in patients with newly diagnosed glioblastoma was not associated with any significant increase in systemic toxic effects compared with temozolomide therapy alone (Table 2). The overall incidence, distribution, and severity of adverse events were similar in patients treated with TTFIELDS plus temozolomide and in those treated with temozolomide alone. The only notable exception was a higher incidence rate of localized skin toxicity (medical device site reaction beneath the transducer arrays) in patients treated with TTFIELDS plus temozolomide. Mild to moderate skin irritation was observed in 43% of patients treated with TTFIELDS plus temozolomide and severe skin reaction (grade 3) in 2%. Mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFIELDS plus temozolomide and occurred mainly at the time of therapy initiation. The incidence of seizures was almost identical in the 2 groups (15 [7%] in the TTFIELDS plus temozolomide group vs 8 [8%] in temozolomide alone group). A total of 12 patients died of causes considered unrelated to treatment while receiving adjuvant therapy (8 [3.9%] in the temozolomide plus TTFIELDS group and 4 [4.0%] in the temozolomide alone group; Table 2).

Discussion

Glioblastoma is a highly aggressive brain tumor affecting men and women, frequently at the peak of life. Prognosis remains poor with no major treatment advance in more than a decade. In the interim analysis of this randomized clinical trial,

the addition of TTFields to standard maintenance temozolomide significantly improved progression-free and overall survival. The prespecified analyses revealed that patients randomized to receive TTFields plus temozolomide compared with patients randomized to receive temozolomide alone had a median progression-free survival of 7.1 months vs 4.0 months (ITT analyses). Patients who received TTFields plus temozolomide had a median overall survival of 20.5 months compared with 15.6 months in those who received temozolomide alone (as per the prespecified per-protocol analysis; the ITT analysis did not differ substantially).

Based on the results of this planned interim analysis, the trial's independent data and safety monitoring committee recommended termination of the trial. Because almost all patients had been enrolled (695/700) in the study by the time the recommendation was implemented, the full trial population will be followed up for both progression-free and overall survival. Subsequent analyses of all secondary end points and subgroups will be performed when the follow-up data are available.

The trial population and the results in the control group in this study were comparable with other glioblastoma clinical trials. Nevertheless, patients in this trial were randomized only after the end of radiochemotherapy, and for most, the first cycle of maintenance temozolomide had been started at the time of randomization; thus, patients with early tumor progression during radiochemotherapy were excluded. Most glioblastoma trials have reported survival from the date of initial diagnosis or study enrollment before starting radiochemotherapy, thus 3 to 4 months before randomization of the current study.

When the interval from diagnosis to randomization is added to the outcome results in this study, the progression-free survival of 7.8 months in the control group is comparable with most other reported studies, and supports the generalizability of these results. The Radiation Therapy Oncology Group (RTOG) 0525 protocol randomized patients only after the end of treatment with temozolomide and radiotherapy, similar to our study.³ The control groups with standard dose temozolomide only in these 2 trials were comparable: progression-free survival from randomization of 4.0 months in the present study and 5.5 months in the RTOG 0525 trial and overall survival of 16.6 months in both trials. Thus, the benefit observed with TTFields cannot be simply attributed to patient selection. In the present trial, the gain of 3 months in both median progression-free survival (from 4.0 months to 7.2 months; HR, 0.62) and median overall survival (from 16.6 months to 19.6 months; HR, 0.74), translating into a survival gain at 2 years of 14% (from 29% to 43%) in the ITT population is in the range of benefit that is considered clinically meaningful for therapeutic agents in oncology.

The prespecified analysis for overall survival in the interim analysis was to be based on the per-protocol population (n = 280); ie, removal in both study groups of the patients who did not start their second course of maintenance temozolomide or had major protocol violations. This analysis met the prespecified threshold for efficacy in the interim analysis for the per-protocol population. In a more conserva-

Table 2. Grade 3 to 4 Treatment-Emergent Adverse Events

	No. (%) of Patients With Adverse Events ^a	
	TTFields Plus Temozolomide (n = 203) ^b	Temozolomide Alone (n = 101) ^c
Hematological disorders ^d	25 (12)	9 (9)
Anemia	1 (<1)	2 (2)
Leukopenia or lymphopenia	11 (5)	5 (5)
Neutropenia	6 (3)	1 (1)
Thrombocytopenia	19 (9)	3 (3)
Cardiac disorders	2 (1)	3 (3)
Eye disorders	2 (1)	1 (1)
Gastrointestinal disorders ^d	11 (5)	2 (2)
Abdominal pain	2 (1)	0
Constipation	2 (1)	0
Diarrhea	1 (<1)	2 (2)
Vomiting	3 (1)	1 (1)
General disorders	17 (8)	5 (5)
Fatigue	8 (4)	4 (4)
Infections	10 (5)	5 (5)
Injury and procedural complications ^d	14 (7)	5 (5)
Fall	6 (3)	2 (2)
Medical device site reaction	4 (2)	0
Metabolism and nutrition disorders	7 (3)	3 (3)
Musculoskeletal disorders	8 (4)	3 (3)
Nervous system disorders ^d	45 (22)	25 (25)
Seizure	15 (7)	8 (8)
Headache	4 (2)	2 (2)
Psychiatric disorders ^d	9 (4)	3 (3)
Anxiety	2 (1)	0
Bradycardia	0	1 (1)
Confusional state	2 (1)	1 (1)
Mental status changes	4 (2)	1 (1)
Psychotic disorder	2 (1)	0
Respiratory disorders	4 (2)	1 (1)
Skin disorders	0	1 (1)
Vascular disorders ^d	8 (4)	8 (8)
Deep vein thrombosis	1 (<1)	3 (3)
Pulmonary embolism	4 (2)	6 (6)

Abbreviation: TTFields, tumor-treating fields.

^a Safety is reported on patients who have received any treatment. Randomized patients who never received any maintenance therapy were excluded from this safety analysis.

^b Eight patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and infection; and 4 patients with central nervous system disorders likely due to tumor progression).

^c Four patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and unknown).

^d Patients may have had more than 1 adverse event so subcategories do not total and not all events are subcategorized.

tive analysis using the ITT population, an overall survival benefit was also manifest. Furthermore, an analysis of robustness performed on all randomized patients enrolled at the time

of study termination (eAppendix 1 in Supplement 2) supports the conclusions of the interim analysis.

This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

This analysis reports a planned interim analysis on data from the first 315 patients with at least 18 months of follow-up; however, for detailed and meaningful subgroup analyses, the mature data of the full data set will be needed. Treatment failure patterns, effects of second-line therapies, and additional molecular analyses on baseline tumor biopsies will allow for better understanding of the clinical effects of this novel treatment modality. With the last patient randomized on November 29, 2014, however, these data are not expected before the end of 2016.

This was an open-labeled study. A sham or placebo treatment for the control group was considered neither practical (patients would be able to sense heat when they were receiving TTFields) nor appropriate (due to the burden for patients and caregivers and the need to shave the scalp and have transducer arrays placed). In this respect, the trial resembles studies evaluating radiation therapy. This raises the question of a placebo effect leading to the improved outcome. Although some effect of placebo may be expected on subjective end points, such as cognitive function and quality of life, objective end points, such as overall and progression-free survival (assessed by a blinded review panel), are independent of pla-

cebo effects in cancer therapy.²⁴ The panel did not have information on treatment received and no stigmata of TTFields array pads were evident on MRI.

Recent randomized studies of patients with glioblastoma, which did not use placebo controls, failed to show any increase in progression-free or overall survival^{3,7} despite intensive treatment regimens requiring twice weekly hospital visits.⁷ The magnitude of effect size seen in the present trial (HR of 0.62 for progression-free survival and 0.74 for overall survival) is beyond what could be attributed to a placebo effect. In addition, the support provided to patients in the TTFields plus temozolomide group by device support specialists during the trial was largely technical in nature and did not include medical supportive care. Medical follow-up with monthly visits was the same for both treatment groups.

Because TTFields were applied only to the head, an increase in systemic adverse events was neither seen nor expected. No increase in seizure rate or neurological adverse events was observed. Almost half of the patients treated with TTFields did experience some grade 1 to 2 (mild to moderate) localized skin reaction related to the application of the transducer arrays used to deliver the TTFields. This adverse effect could be managed using published skin care guidelines for patients receiving TTFields.²⁵ Only 2% of patients receiving TTFields had grade 3 to 4 (severe) skin reactions beneath the transducer arrays.

Conclusions

In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

ARTICLE INFORMATION

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New Jersey Neuroscience Institute, Edison (Landolfi); Maine Medical Center, Portland (Desai); Fondazione Ospedale Maggiore Policlinico, Milan, Italy (Caroli); Houston Methodist Hospital, Houston, Texas (Kew); Hospices Civils de Lyon, University Claude Bernard Lyon 1, Lyon, France (Honnorat); Novocure, Haifa, Israel (Kliron, Weinberg, Palti).

Author Contributions: Drs Stupp and Ram had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Stupp, Kirson, Weinberg, Palti, Ram.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Stupp, Kirson, Ram.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Steinberg.

Obtained funding: Palti.

Administrative, technical, or material support: Stupp, Kirson, Weinberg, Hegi, Ram.

Study supervision: Stupp, Kirson, Weinberg, Hegi, Ram.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for

Disclosure of Potential Conflicts of Interest. Dr Stupp reported receiving travel assistance from Novocure for data review and presentation of the results at medical meetings; and receiving personal fees for serving on advisory boards for Roche/Genentech, Merck KGaA, Merck & Co, and Novartis. Dr Taillibert reported receiving personal fees from Mundipharma EDO and Roche. Dr Kanner reported receiving institutional grant funding and personal fees for speaking and device training from Novocure. Dr Kesari reported receiving institutional grant funding and personal fees for consulting and attending advisory meetings from Novocure. Dr Steinberg reported receiving consulting fees from Novocure for performing the statistical analysis. Dr Toms reported receiving personal fees from Novocure for serving on an advisory board. Dr Lieberman reported receiving institutional grant funding from Novocure. Dr Fink reported receiving personal fees from Novocure for serving on an advisory board; and receiving personal fees from Genentech for serving in the speakers program. Dr Zhu reported receiving institutional grant funding and personal fees from Novocure. Dr Engelhard reported receiving institutional grant funding and personal fees from Novocure. Dr Chen reported receiving grant funding, personal fees, nonfinancial support, and being a stock holder and chief

oncology officer in Pharmo-kinesis; and receiving grant funding, personal fees, nonfinancial support, and being a stock holder in and CEO of NeOnc Technologies. Dr David Tran reported receiving grant funding from Celldex, NWBiotech, Novocure, and Merck; and receiving personal fees from Novocure and PRIME Oncology. Dr Hottinger reported receiving travel reimbursement and speakers fees from Novocure and Merck Sharp & Dohme; and receiving personal fees for serving on an advisory board for Roche. Dr Landolfi reported receiving personal fees from Novocure for serving on an advisory board. Dr Honnorat reported receiving trial support from Novocure and serving on an advisory board for Novocure. Dr Idhah reported receiving grants from Fondation ARC pour la recherche sur le Cancer; receiving research support from IntselChimos and Beta-Innov; receiving personal fees from Novartis for attending a conference; receiving travel reimbursement from Hoffmann-La Roche; and serving as an editorial advisory board member for *Le Lait du Cancérologue*. Drs Kirson, Weinberg, and Palti reported being employees of Novocure. Dr Palti also reported holding 35 issued US patents and minority stock ownership in Novocure. Dr Hegi reported receiving institutional grant funding from Novocure, Merck Sharp & Dohme, Roche, and Merck-Serono; and nonfinancial support from MDxHealth for sample testing. Dr Ram reported receiving institutional grant funding from Novocure; and serving as a paid consultant for and holding stock options in Novocure. Drs Taylor, Silvani, Barnett, Henson, Sroubek, Nam Tran, Desai, Caroli, and Kew reported having no disclosures.

Funding/Support: The study was funded by Novocure Ltd.

Role of the Funder/Sponsor: Novocure Ltd had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The study was designed by the first and last authors (R.S. and Z.R.), together with representatives from Novocure (mainly E.D.K.). The study oversight was supported and monitored by a clinical research organization (CRO), who also holds the database. Data were collected by the investigators and monitored by the CRO. Device use data were downloaded monthly and transferred to the study investigators or their research staff by device support specialists from Novocure Ltd. The data were analyzed separately by the statistician of the independent data monitoring committee and the study statistician (D.M.S.). Data interpretation was the responsibility of the first and last authors (R.S. and Z.R.), together with the study sponsor representative and project lead (E.D.K.). These 3 physicians also jointly developed the first draft. A subsequent mature draft and a prefinal version were circulated among all authors who gave additional input, contributed to, and approved the manuscript. The first and last authors (R.S. and Z.R.) and E.D.K. had full access to all data, and also reviewed all patient profiles for consistency (R.S. and E.D.K.). The decision to publish the data followed the independent data and safety monitoring committee recommendation for data release, and was supported by all coauthors.

The roles of employees of Novocure are described in the respective author contributions. Other employees' involvement was limited to technical support of the device.

Additional Contributions: We thank the patients and their families for participating in the trial. We are grateful to all of the EF-14 investigators, who are listed in eAppendix 4 in Supplement 2, and the nursing staff for taking care of the patients.

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Indications For Use and Safety Information in the United States:

Please visit www.optune.com/IFU for Optune Instructions For Use (IFU) for complete information regarding the device's indications, contraindications, warnings and precautions.

Optune is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune is indicated following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Summary of Important Safety Information**Contraindications**

Do not use Optune in patients with an active implanted medical device, a skull defect (such as: missing bone with no replacement), or bullet fragments. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune in patients that are known to be sensitive to conductive hydrogels. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions

Optune can only be prescribed by a healthcare provider that has completed the required certification training provided by Novocure (the device manufacturer).

Do not prescribe Optune for patients that are pregnant, you think might be pregnant or are trying to get pregnant, as the safety and effectiveness of Optune in these populations have not been established.

The most common ($\geq 10\%$) adverse events involving Optune in combination with temozolomide were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression.

Use of Optune in patients with an inactive implanted medical device in the brain has not been studied for safety and effectiveness, and use of Optune in these patients could lead to tissue damage or lower the chance of Optune being effective.

If the patient has an underlying serious skin condition on the scalp, evaluate whether this may prevent or temporarily interfere with Optune treatment.

Indications for use and safety information in Europe:**Newly diagnosed GBM**

Optune is intended for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant temozolomide, concomitant to maintenance temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant temozolomide. Treatment may be given together with maintenance temozolomide (according to the prescribing information in the Temodar package insert) and after maintenance temozolomide is stopped.

Recurrent GBM

Optune is intended for the treatment of patients with recurrent GBM who have progressed after surgery, radiotherapy and temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy or chemotherapy.

Contraindications

Do not use Optune if you are pregnant, think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune was not tested in pregnant women. Do not use Optune if you have clinically significant hepatic, renal or haematologic disease. Do not use Optune if you have significant additional neurological disease (primary seizure disorder, dementia, progressive degenerative neurological disorder, meningitis or encephalitis, hydrocephalus associated with increased intracranial pressure). Do not use Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Treatment Kit may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions

Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). All servicing procedures must be performed by qualified and trained personnel.

Do not use Optune Treatment Kit if you are 17 years old or younger. The system has not been tested in persons 17 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

Do not wet the device or the transducer arrays. Do not use any parts that do not come with the Optune treatment kit, or that were not sent to you by the device manufacturer or given to you by your doctor.

Optune commonly causes skin irritation beneath the transducer arrays and in rare cases lead to headaches, falls, fatigue, muscle tw itching or skin ulcers.

For complete information regarding Optune's indication, contraindication, warnings and precautions please see the Instructions for Use (IFU). (<http://www.optune.com/deutsch/materialien/schulungen.asp>)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 05, 2015

Novocure, Ltd.
% Mr. Jonathan S. Kahan
Partner
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Re: P100034/S013
Trade/Device Name: Optune™ (Formerly the NovoTTF-100A System)
Filed: April 10, 2015
Amended: July 23, 2015
Product Code: NZK

Dear Mr. Jonathan S. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the Optune™ (formerly the NovoTTF-100A System). This device is indicated as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. Optune™ was previously approved in 2011 for the treatment of recurrent GBM with the following Indications for Use (IFU): Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted. We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is

therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, <http://www.fda.gov/udi>.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm>

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at <http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm>

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm>. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

Page 4 – Mr. Jonathan S. Kahan

P100034/S013

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center - WO66-G609
10903 New Hampshire Avenue
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If you have any questions concerning this approval order, please contact Daryl Kaufman at 301-796-6467 or Daryl.Kaufman@fda.hhs.gov.

Sincerely yours,

Carlos L. Pena -S

Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
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Center for Devices and Radiological Health



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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NovoCure, Ltd.
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APR 8 2011

Re: P100034
NovoTTF-100A System
Filed: August 16, 2010
Amended: September 10, October 19, December 13, and December 27, 2011; and
February 17, and April 8, 2011
ProcCode: NZK

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the NovoTTF-100A System. This device is indicated for treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme, following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(D)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(g) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

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Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the conditions outline above, you must conduct the following post-approval study (PAS):

The New Enrollment Study for NovoTTF-100A in Recurrent GBM Patients: Per agreed on study outline (e-mail dated April 5, 2011) this study will address the following question: Is the overall survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)? This question will be addressed with a prospective, multi-center, non-randomized, unblinded, concurrent control study of NovoTTF-100A in recurrent Glioblastoma Multiforme (GBM) patients. The study will be conducted in at least 30 sites, at least half of them in the United States, and may include centers with previous experience with the device. Patients 22 years old and older will be included in the PAS. A total of 486 subjects will be enrolled, with 243 subjects per study arm. All study participants will be followed until death. Study follow-up visits include baseline and monthly in-office visits until disease progression. Assessment at baseline includes the Mini Mental State Examination (MMSE) and genetic profiling. The monthly assessments include survival status, MMSE and adverse events assessment. After disease progression study participants will be followed by monthly phone calls to determine survival status.

The primary data analysis will compare overall survival in NovoTTF-100A patients to that seen in concurrent BSC comparison patients, in the investigational device exemption (IDE) study Intent-to-Treat population, within a predefined confidence interval bound consistent with a performance goal of 1:375. The secondary endpoints will be: Change in neuro-cognitive function from baseline based on the MMSE; Genetic profiling of tumors and correlation with response to NovoTTF-100A treatment, specifically:

- MGMT promoter methylation status
- EGFR amplification, over expression or rearrangement
- Chromosomes 1p/19q deletion status
- Adverse event incidence by body system and term, including:
- Incidence of seizures
- Anticonvulsant use

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Please be advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

In addition to the Annual Report requirements, FDA would like to remind you that you are required to submit PAS Progress Reports every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order"

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm>

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order"

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2>

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process"

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm>

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

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device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportsProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

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All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information:

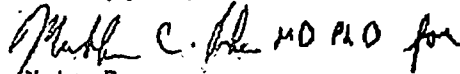
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/Pre-marketSubmissions/ucm134508.htm>; clinical and statistical data:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/Pre-marketSubmissions/ucm136377.htm>)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center -- WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Ms. Jan C. Callaway at 301-796-5620.

Sincerely yours,



Christy Foreman

Acting Director

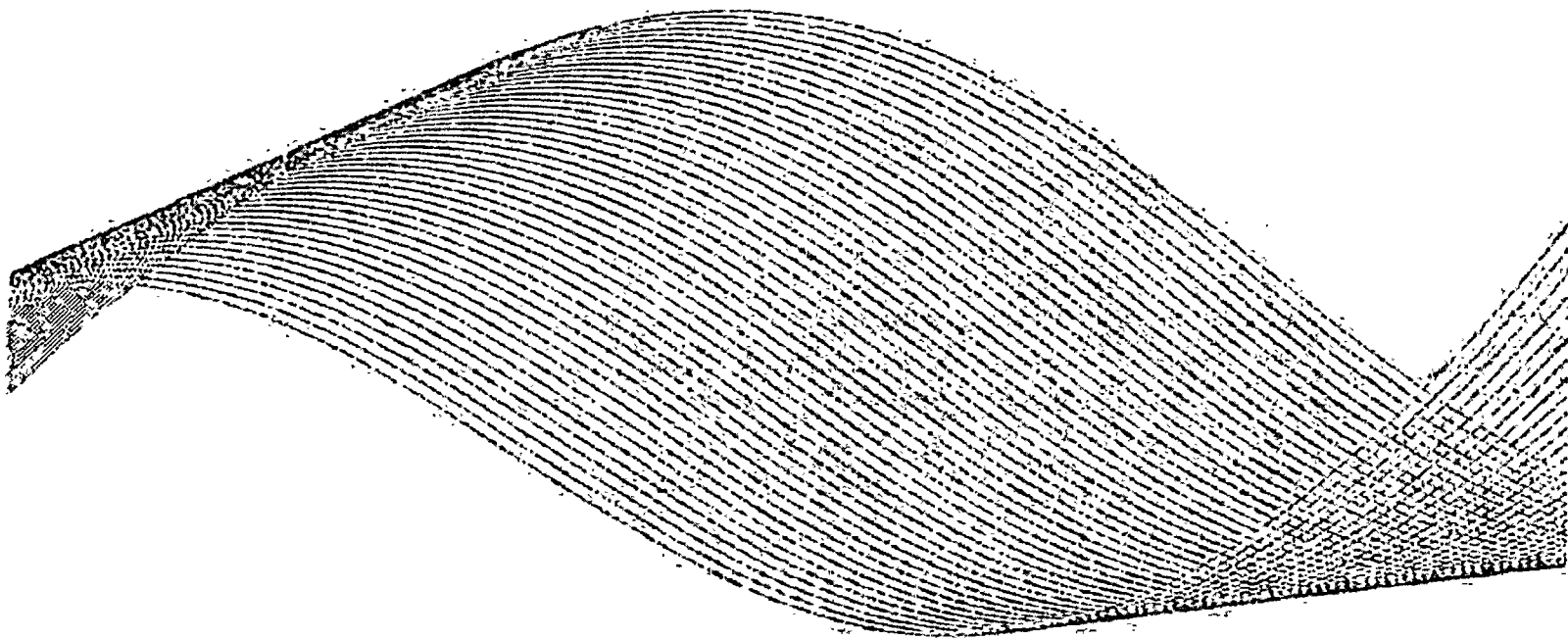
Office of Device Evaluation

Center for Devices and Radiological Health

Food and Drug Administration



INSTRUCTIONS FOR USE



novocure™

This manual is intended for physicians prescribing the use of Optune.
Additional information is found in the following materials:
• Patient Information and Operation Manual

Caution: Federal law restricts this device to sale by or on the order of a physician

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Indications for Use

Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune™ is indicated following histologically or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Contraindications, Warnings and Precautions

Contraindications

Do not use Optune if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement) or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

Warning – Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). Ask to see a certificate signed by Novocure that says they completed a training course. Your training will include a detailed review of this manual and practice in the use of the system. In addition, you will be trained in what to do if there are problems with treatment. Use of Optune without receiving this training can result in breaks in treatment and may rarely cause increased scalp rash, open sores on your head, allergic reactions or even an electric shock.

Warning – Optune is not intended to be used as a substitute for chemotherapy but rather as an adjunct to treatment with TMZ for newly diagnosed GBM.

Warning – Do not use Optune if you are 21 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

Warning – Do not use Optune if you are pregnant, you think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant or if it will be effective.

Warning – In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), use high potency topical steroids (hydrocortisone cream) when replacing transducer arrays. This will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin break down, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals. Taking a break from treatment may lower your chance to respond to treatment.

Warning – All servicing procedures must be performed by qualified and trained personnel. If you attempt to open and service the system alone you may cause damage to the system. You could also get an electric shock by touching the inner parts of the device.

Precautions

Caution – Keep Optune out of the reach of children. If children touch the device, they could damage the device. This could cause a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution – Do not use any parts that do not come with the Optune Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution – If your doctor used plates or screws to close your skull bone during your surgery, be careful when placing the transducer arrays. Make sure the round disks that make up the transducer arrays are not on top of the areas where you can feel the screws or plates under your skin. In other words, make sure the screws or plates under your skin are in between the round disks that make up the transducer arrays. If you do not do this, you may have increased skin damage which may lead to a break in treatment. Breaks in treatment may lower the chance of the device being effective.

Caution – Tell your doctor before using the device if you have an inactive implanted medical device in the brain (for example, stents, plastic drug delivery reservoirs, aneurysm clips or coils, device leads). Use of Optune in subjects with inactive implanted medical devices in their brain was not been tested and could lead to tissue damage or lower the chance of the device being effective.

Caution – Do not use Optune if any parts look damaged (loose wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Use of damaged components can damage the device, and cause a break in treatment. Breaks from treatment may lower your chance to respond to treatment.

Caution – Do not wet the device or transducer arrays. Getting the device wet may damage it, preventing you from receiving treatment for the right amount of time. Getting the transducer arrays very wet is likely to cause the transducer arrays to come loose from your head. If this happens, the device will turn off and you will need to change the transducer arrays.

Caution - Before connecting or disconnecting the transducer arrays, make sure that the Optune power switch is in the OFF position. Disconnecting transducer arrays with the device power switch in the ON position may cause a device alarm to go off, and could damage the device.

Caution - If you have an underlying serious skin condition on the scalp, discuss with your doctor whether this may prevent or temporarily interfere with Optune treatment.

Notices

Notice! The Optune device and transducer arrays will activate metal detectors.

Notice! Do not use Optune if your tumor is located in the lower parts of the brain close to the spinal cord. Ask your doctor if your tumor is located in this part of your brain. Optune has not been tested in patients with tumors in these locations. It is unknown whether these tumors will respond to treatment.

Notice! You should use Optune for at least 18 hours a day to get the best response to treatment. Using Optune for less than 18 hours a day lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune before you finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune even if you have used it less than the recommended 18 hours per day. You should stop using the device only if your doctor tells you to. Stopping treatment could lower the chances that you will respond to treatment.

Notice! If you plan to be away from home for more than 2 hours, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Make sure you have at least 12 extra transducer arrays at all times. This will last you until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left. If you do not order transducer arrays in time you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1.5 hours from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! You should carry the Troubleshooting Guide (Section 26) at all times. This guide is necessary to ensure Optune works properly. If you do not work the system correctly you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Do not block the device vents located on the sides of the Optune device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device.

Notice! Do not block the battery charger vents located on the front of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging.

Notice! Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off.

Notice! The transducer arrays are for single use and should not be taken off your head and put back on again. If you put a used transducer array back on your head again, it may not stick well to your skin and the device could turn off.

Description

Optune, for the treatment of newly diagnosed and/or recurrent GBM, is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields ("TTFields") within the human body. TTFields are applied to the patient by electrically-insulated surface transducer arrays. TTFields disrupt the rapid cell division exhibited by cancer cells¹.

Optune is comprised of two main components: (1) an Electric Field Generator (the Optune device); and (2) INE Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included in the Optune Treatment Kit: power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

Treatment parameters are preset by Novocure such that there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week and the scalp re-shaved in order to maintain optimal contact. Patients carry the device in an over-the-shoulder bag or backpack and receive continuous treatment without changing their daily routine.

1 Kirson, E. D., V. Djalil, et al. (2007). "Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors." *Proc Natl Acad Sci U S A* 104(24): 10152-7.

Principles of Operation

Optune produces alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp.

TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTField technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM).

In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. It is noted that, because TTFields are only applied to the brain, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature. Thus, TTField application has the advantage of being highly selective and is not expected to be associated with significant toxicity.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature.

Preclinical Data

TTFields have been shown both in vitro and in vivo to effectively inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to effectively inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed), due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase².

Specifically, TTFields have been shown to inhibit glioblastoma cells in vitro and in vivo at a frequency of 200 kHz and an intensity of 0.7 V/cm. Based on realistic finite element mesh simulations and direct measurements of TTFields intensity in experimental animals, and in the human brain, Novocure has concluded that effective TTField intensities can be generated in the brains of large animals and humans. Extensive safety studies in healthy animals (mice, rats and rabbits) have shown that TTFields are not associated with significant systemic toxicities. Neither acute, nor chronic systemic toxicities were seen when TTFields were applied to the torso or head, at different frequencies (100-200 kHz), different intensities and for different periods of time³.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for Optune has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

2 Kirson, E. D., & Gurvich, et al. (2004). "Disruption of cancer cell replication by alternating electric fields." *Cancer Res* 64(9): 3288-95.
3 Kirson, E. D., V. Dooly, et al. (2007).

Clinical Data

NEWLY DIAGNOSED GLIOBLASTOMA (see page 17 for recurrent GBM)

Pilot Clinical Study in Newly Diagnosed GBM

Optune together with temozolomide (TMZ) has been tested in ten newly diagnosed GBM subjects in a single center, pilot study in Europe. Median progression free survival (PFS) of the patients in this study exceeded historical controls (14.4 months versus 7.1 months, respectively). At the end of the study (4 years from initiation) 5 of the 10 patients died; of the remaining 5 patients 2 were lost to follow up and 3 were reported alive and progression free. Median OS from diagnosis was greater than 40 months (compared to 14.7 months in historical controls). The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device transducer arrays.

Pivotal Clinical Study in Newly Diagnosed GBM

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of newly diagnosed GBM subjects treated with Optune and Temozolomide (TMZ) to those treated with TMZ alone.

The following were the objectives of the study:

To prospectively compare the progression free survival and overall survival of newly diagnosed GBM subjects treated with Optune and TMZ to those treated TMZ alone.

To collect evidence of the safety of TTFIELDS applied to subjects with newly diagnosed GBM using Optune

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows

Inclusion Criteria

- a. Pathological evidence of GBM using WHO classification criteria.
- b. ≥ 18 years of age.
- c. Received maximal debulking surgery and radiotherapy concomitant with Temozolomide (45-70Gy).
 - 1) Patients may enroll in the study if received Gliadel wafers before entering the trial
 - 2) Any additional treatments received prior to enrollment will be considered an exclusion
 - 3) Minimal dose for concomitant radiotherapy is 45 Gy
- d. Karnofsky scale ≥ 70
- e. Life expectancy at least 3 months
- f. Participants of childbearing age must use effective contraception.
- g. All patients must sign written informed consent
- h. Treatment start date at least 4 weeks out from surgery.
- i. Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant Temozolomide or radiotherapy

Exclusion Criteria

- a. Progressive disease (according to MacDonald Criteria). If pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression.
- b. Actively participating in another clinical treatment trial
- c. Pregnant
- d. Significant co-morbidities at baseline which would prevent maintenance Temozolomide treatment.
 - 1) Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
 - 2) Neutropenia (absolute neutrophil count $< 1.5 \times 10^3/\mu\text{L}$)
 - 3) CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)
 - 4) Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
 - 5) Total bilirubin $>$ upper limit of normal
 - 6) Significant renal impairment (serum creatinine $> 1.7 \text{ mg/dL}$)
- e. Implanted pacemaker, programmable shunts, denbrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias
- f. Intra-tentorial tumor
- g. Evidence of increased intracranial pressure (midline shift $> 5\text{mm}$, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
- h. History of hypersensitivity reaction to Temozolomide or a history of hypersensitivity to CTC

Study Procedures:

Treatment Arm

Optune was given together with maintenance TMZ. At treatment initiation patients were seen at an outpatient clinic. During this visit baseline examinations were performed and Optune treatment initiated. The patients were instructed on the operation of Optune and battery replacement. Once the patients were trained in operating the device they were released to continue treatment at home. The patients received multiple 1 month courses of continuous Optune treatment. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Follow-up

During treatment all patients were seen once every month at an outpatient clinic where they underwent medical follow-up and routine laboratory exams. An MRI was performed every second month following the baseline MRI until second progression or 24 months (whichever came first, when treatment on both arms of the study was terminated). In the case of clinical progression an unscheduled MRI was obtained within 1 week of the investigator becoming aware of the clinical progression. No additional MRIs were required after second progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality was assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Analyses: Two analyses were performed in the study: An interim analysis on the first 315 patients with a minimum of 18 months follow up and a final analysis on the full study cohort of 695 patients.

Protocol Deviations: Major protocol deviations were defined as deviations that have the potential to influence the primary and secondary efficacy endpoints of the study. There were a total of 13 major protocol deviations in the interim analysis and a total of 24 major protocol violations at the final analysis.

In the interim analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 11 patients in the TMZ alone arm received Optune treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

In the final analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 22 patients in the TMZ alone arm received Optune treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

Analysis Populations: Progression free survival was analyzed in the intent to treat (ITT) population which included all randomized subjects (210 Optune / TMZ and 105 TMZ alone at the interim analysis, 466 Optune / TMZ and 229 TMZ alone at the final analysis). Overall survival was analyzed in the per protocol (PP) population which included all patients receiving at least the first course of TMZ and had no major protocol deviations (196 Optune / TMZ and 84 TMZ alone at the interim analysis; 429 Optune / TMZ and 180 TMZ alone at the final analysis). Major protocol deviations included patients who received other experimental therapies on protocol or crossed over from the TMZ alone arm to Optune / TMZ.

Subject Characteristics: 315 subjects (210 Optune/TMZ; 105 TMZ) with newly diagnosed GBM were enrolled in the interim analysis of the study. Baseline characteristics in the ITT population were as follows:

Baseline Characteristic	Treatment Group	
	Optune/TMZ	TMZ Alone
	(N=210) n(%)	(N=105) n(%)
Gender		
Male	140 (66.67)	67 (63.81)
Female	70 (33.33)	38 (36.19)
Central MGMT Assessment		
Invalid	24 (11.43)	11 (10.48)
Unknown	58 (27.62)	30 (28.57)
Methylated	49 (23.33)	26 (24.76)
Unmethylated	79 (37.62)	38 (36.19)
Extent of Resection		
Biopsy	23 (10.95)	11 (10.48)
Gross Total Resection	135 (64.29)	67 (63.81)
Partial Resection	52 (24.76)	27 (25.71)
Area		
ROW	83 (39.52)	41 (39.05)
USA	127 (60.48)	64 (60.95)
Tumor Position		
Missing	0 (0)	3 (2.86)
Corpus Callosum	12 (5.71)	3 (2.86)
Frontal Lobe	64 (30.48)	32 (30.48)
Occipital Lobe	7 (3.33)	4 (3.81)
Parietal Lobe	35 (16.67)	27 (25.71)
Temporal Lobe	92 (43.81)	36 (34.29)
Tumor Location		
Missing	0 (0)	1 (0.95)
Both	2 (0.95)	1 (0.95)
Corpus Callosum	8 (3.81)	3 (2.86)
Left	93 (44.29)	41 (39.05)
Right	107 (50.95)	59 (56.19)
Karnofsky Performance Score	Median	90
	Min, Max	60, 100
Age in Years	Median	57
	Min, Max	20, 83
No. of Cycles of TMZ Received	Median	6
	Min, Max	1, 26
No. of Cycles of Optune Received	Median	9
	Min, Max	1, 58
Time from GBM Diagnosis to Randomization (Days)	Median	115
	Min, Max	59, 171

As seen above, all baseline characteristics are well balanced between arms in the ITT population at the interim analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 35 patients (11.11%) had tissue that was not evaluable, and 88 patients (27.94%) did not have tissue available for analysis.

695 subjects (466 Optune / TMZ; 229 TMZ alone) with newly diagnosed GBM were enrolled in the study and had CRF information available at the time of the final analysis. Baseline characteristics in the ITT population were as follows:

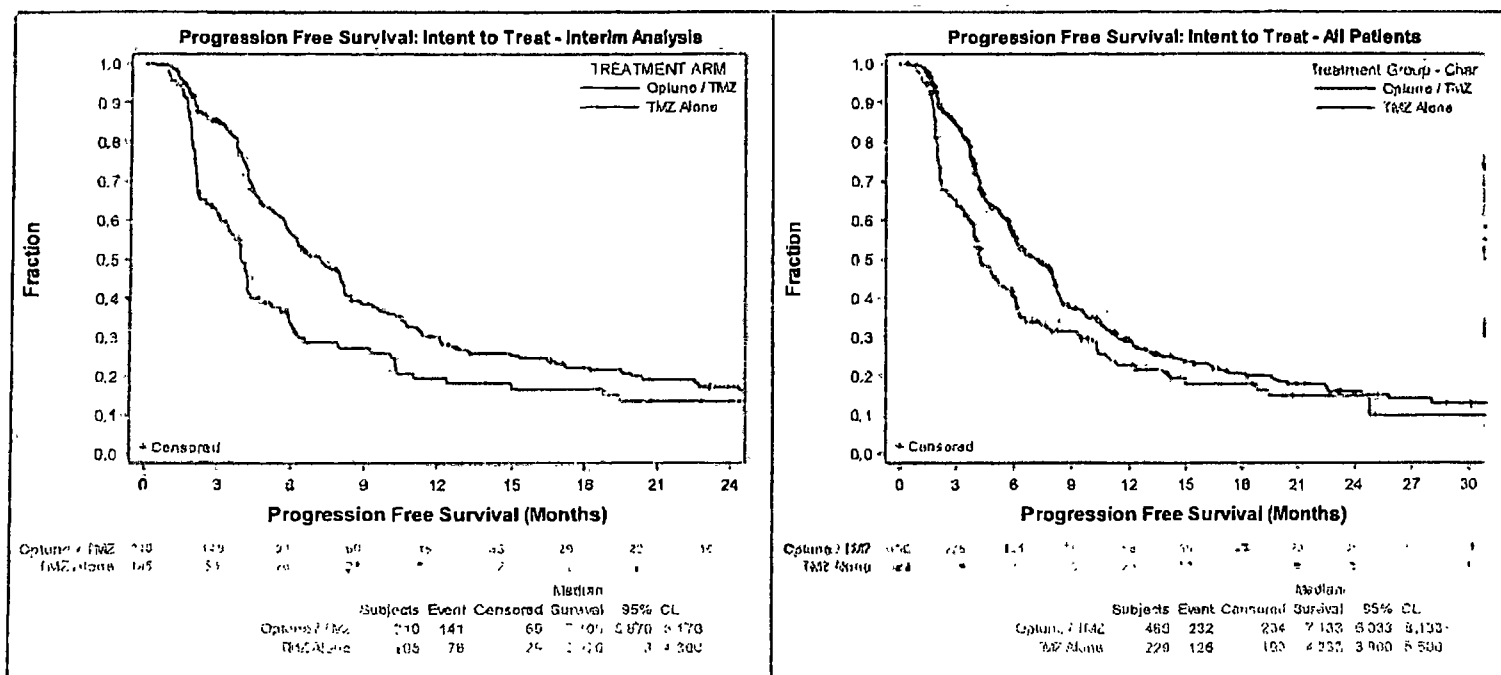
Baseline Characteristic		Treatment Group	
		Optune/TMZ	TMZ Alone
		(N=466) n(%)	(N=229) n(%)
Gender			
	Male	316 (67.81)	157 (68.56)
	Female	150 (32.19)	72 (31.44)
Central MGMT Assessment			
	Invalid	46 (9.67)	18 (7.86)
	Unknown	106 (22.75)	57 (24.89)
	Methylated	127 (27.25)	67 (29.26)
	Unmethylated	187 (40.13)	87 (37.99)
Extent of Resection			
	Biopsy	61 (13.09)	30 (13.1)
	Gross Total Resection	253 (54.29)	124 (54.15)
	Partial Resection	152 (32.62)	75 (32.75)
Area			
	ROW	245 (52.58)	111 (48.47)
	USA	221 (47.42)	118 (51.53)
Tumor Position			
	Missing	51 (6.65)	15 (6.55)
	Corpus Callosum	21 (4.51)	9 (3.93)
	Frontal Lobe	142 (30.47)	67 (29.26)
	Occipital Lobe	14 (3)	4 (1.75)
	Parietal Lobe	77 (16.52)	50 (21.83)
	Temporal Lobe	181 (38.84)	84 (36.68)
Tumor Location			
	Missing	30 (6.44)	12 (5.24)
	Both	12 (2.58)	3 (1.31)
	Corpus Callosum	12 (2.58)	7 (3.06)
	Left	193 (41.42)	93 (40.61)
	Right	219 (47)	114 (49.78)
Karnofsky Performance Score	Median	90	90
	Min, Max	60, 100	70, 100
Age in Years	Median	56	57
	Min, Max	19, 83	19, 80
No. of Cycles of TMZ Received	Median	5	4
	Min, Max	1, 26	1, 24
No. of Cycles of Optune Received	Median	6	0
	Min, Max	1, 58	0, 0
Time from GBM Diagnosis to Randomization (Days)	Median	113	111
	Min, Max	59, 498	43, 500

As seen above, all baseline characteristics are well balanced between arms in the ITT population at the final analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 64 patients (9.21%) had tissue that was not evaluable, and 163 patients (23.45%) did not have tissue available for analysis.

Primary Effectiveness Endpoint: Progression Free Survival at the Interim Analysis

The threshold for statistical significance based on the Lan-DeMets O'Brien-Fleming method at the interim analysis was pre-defined as $p=0.01394$, and the test was to be performed in the ITT population according to the protocol. In the ITT population, which included all randomized subjects (Optune/TMZ=210, TMZ alone=105), PFS at the interim analysis met this threshold. The difference of more than 3 months in median PFS is highly clinically significant. The Hazard Ratio for PFS was 0.621, which translates into a 37.9% decrease in the risk of progression when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 695 patients (Optune/TMZ=466, TMZ alone=229), PFS was also highly significant with a hazard ratio of 0.694.

Primary Efficacy Endpoint - Progression Free Survival (ITT)



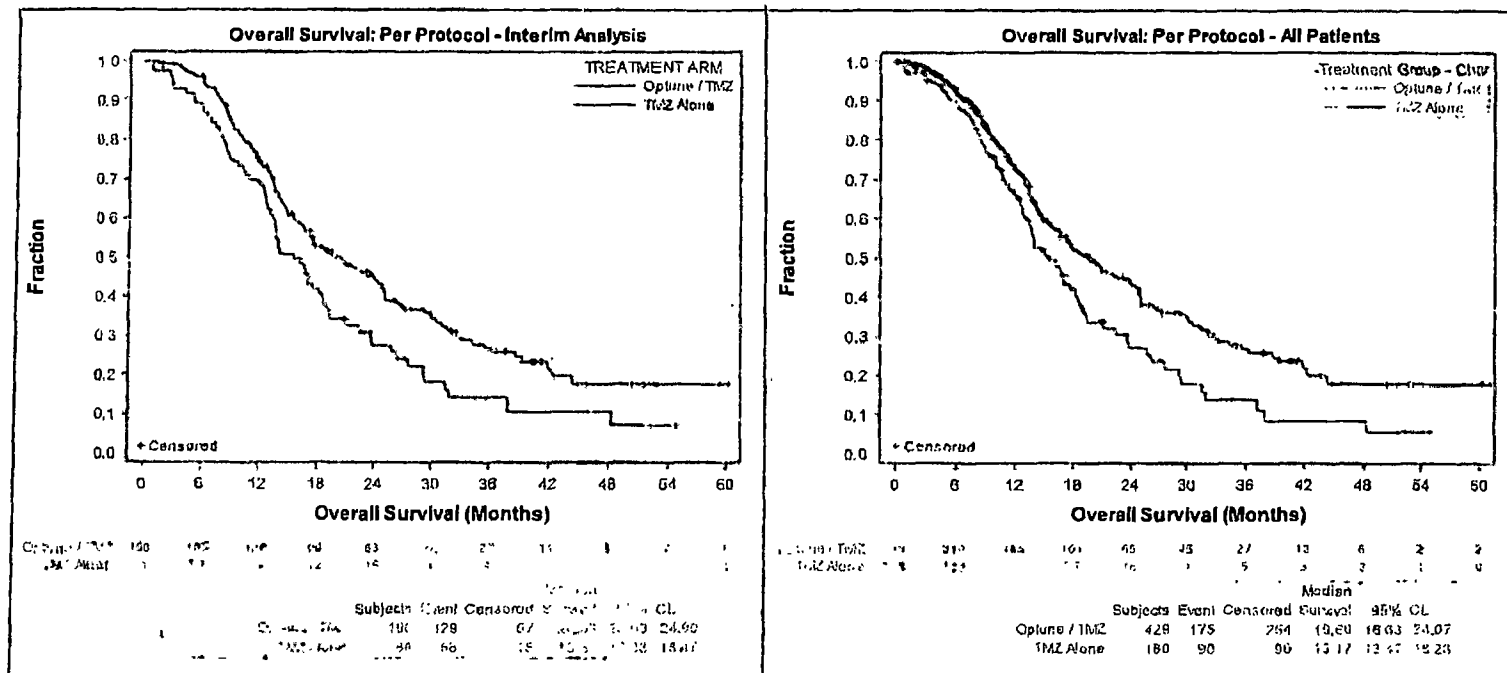
	Interim Analysis		Final Analysis	
	Optune/TMZ	TMZ Alone	Optune/TMZ	TMZ Alone
Median (95% CI)	7.2 (5.9, 8.2)	4.0 (3.0, 4.3)	7.1 (6.0, 8.1)	4.2 (3.9, 5.5)
Log-rank test	$p=0.0013$		$p=0.0010$	
Hazard Ratio (95% CI)	0.621 (0.468, 0.823)		0.694 (0.558, 0.823)	

Although not a pre-specified endpoint, PFS was also analyzed in the PP population at the interim and final analyses. Median PFS in the PP population was identical to the ITT population at the interim analysis and slightly longer than the ITT population at the final analysis. Notably, median PFS remained significantly higher in the Optune/TMZ group than in the TMZ alone group in the PP population at both the interim and final analyses.

Powered Secondary Effectiveness Endpoint: Overall Survival at the Interim Analysis

Overall survival (OS) was a powered secondary analysis in the trial. The threshold for superior OS at the interim analysis was predefined in the protocol at 0.00598 according to the Lan-DeMets O'Brien-Fleming alpha spending function, and was to be tested in the PP population. In the PP population, which analyzed patients according to the treatment they actually received (as treated), Optune/TMZ=196, TMZ=84, OS was also significantly longer in the Optune/TMZ arm compared to the TMZ alone arm. An increase of almost 3 months as seen here is highly significant clinically. The hazard ratio for OS was 0.666. This translates into a 33.4% decrease in the risk of death when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 609 patients (Optune/TMZ=429, TMZ alone=180), OS was also highly significant with a hazard ratio of 0.683.

Overall Survival (PP)



	Interim Analysis		Final Analysis	
	Optune/TMZ	TMZ Alone	Optune/TMZ	TMZ Alone
Median (95% CI)	20.5 (16.6, 24.9)	15.6 (12.9, 18.5)	19.6 (16.6, 24.1)	15.2 (13.5, 18.2)
Log-rank test	p=0.0042		p=0.0030	
Hazard Ratio (95% CI)	0.666 (0.495, 0.898)		0.683 (0.529, 0.882)	

Although not a pre-specified secondary endpoint, OS was also analyzed in the ITT population. At the interim analysis, OS in the ITT population was also significantly longer in the Optune/TMZ arm compared to TMZ alone by almost 20%. The median OS was 19.6 months (95% CI 16.5-24.1) in the Optune/TMZ group and 16.6 months in the TMZ alone group (95% CI 13.5-19.1). An increase of 3 months as seen here is highly significant both statistically (log-rank p=0.0338) and clinically. The hazard ratio for OS was 0.744 using a Cox regression analysis. This translates into a 25.6% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

Furthermore, at the final analysis, OS in the ITT population was also significantly longer in the Optune/TMZ arm compared to TMZ alone by 17%. The median OS was 19.4 months (95% CI 16.5-23.8) in the Optune/TMZ group and 16.6 months in the TMZ alone group (95% CI 13.7-19.5). An increase of almost 3 months as seen here is highly significant statistically and clinically (log-rank p=0.0229). The hazard ratio for OS was 0.754 using a Cox regression analysis. This translates into a 24.6% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

Secondary Endpoints: Secondary endpoints also showed an advantage for Optune/TMZ compared to TMZ alone. The results below are from the interim analysis which included 315 patients (210 Optune/TMZ and 105 TMZ alone).

Endpoint	Optune/TMZ	TMZ Alone	P-Value
Progression Free Survival at 6 months (ITT)	56.7%	33.7%	0.0004
1-year survival (PP)	75%	69%	0.151
2-year survival (PP)	48%	32%	0.0058
Complete response rate (ITT)	9%	3.5%	NA

In addition, although not a pre-specified endpoint, 1- and 2-year survival were also analyzed in the ITT population at the interim analysis. In the ITT population, 1-year survival was 75% in the Optune/TMZ group and 70% in the TMZ alone group (p-value=0.162) at the interim analysis. 2-year survival in the ITT population at the interim analysis was 48% in the Optune/TMZ group and 34% in the TMZ alone group (p-value=0.0122). Furthermore, the 1-year survival rates at the final analysis are shown in the table below:

Endpoint	Optune/TMZ	TMZ Alone	P-Value
1-year survival (PP)	69%	63%	0.131
1-year survival (ITT)	69%	66%	0.265

Quality of Life: Quality of Life assessments were based on the interim analysis cohort of 315 subjects. Quality of life, cognitive function and functional status were all maintained throughout treatment with the device, leading to the clear conclusion that use of Optune does not harm patients' quality of life, cognitive function or ability to perform activities of daily living.

Safety Results: Safety was assessed on all patients at the final analysis who received any treatment at the time of the analysis (Optune/TMZ=437, TMZ alone=207). A slightly higher incidence of grade 1-2 adverse events was seen in some of the systems in the Optune/TMZ arm of the study. This is most likely a reflection of the longer duration of TMZ treatment in these patients (median of 6 cycles versus 4 cycles in the control arm) due to the increase in PFS seen in the treatment group. Grade 3-5 adverse events were well balanced between arms. None of the grade 3-5 adverse events in these body systems were considered related to Optune by any of the investigators except for 1% grade 3 skin irritation.

All Adverse Events by Body System and Severity (Safety Population)

	Optune/TMZ (N=437)			TMZ Alone (N=207)		
System Organ Class	Low-Medium	Severe	Fatal	Low-Medium	Severe	Fatal
Number of Patients with ≥1 AE	214 (49%)	169 (39%)	25 (3%)	91 (44%)	87 (40%)	7 (3%)
Blood and Lymphatic System Disorders	66 (20%)	47 (11%)	0	49 (24%)	21 (10%)	0
Cardiac Disorders	12 (3%)	4 (1%)	5 (1%)	6 (3%)	4 (2%)	0
Ear and Labyrinth Disorders	25 (6%)	0	0	8 (4%)	0	0
Endocrine Disorders	11 (3%)	0	0	4 (2%)	0	0
Eye Disorders	36 (8%)	3 (1%)	0	15 (7%)	2 (1%)	0
Gastrointestinal Disorders	202 (46%)	18 (4%)	0	76 (37%)	4 (2%)	0
General Disorders and Administration Site Conditions	175 (40%)	27 (6%)	1 (<1%)	75 (37%)	10 (5%)	1 (<1%)
Hepatobiliary Disorders	1 (<1%)	1 (<1%)	0	5 (2%)	0	0
Liver Disorder	1 (<1%)	0	0	3 (1%)	0	0
Immune System Disorders	10 (2%)	0	0	7 (3%)	0	0
Infections and Infestations	117 (27%)	19 (4%)	3 (1%)	50 (24%)	6 (3%)	1 (<1%)
Injury, Poisoning and Procedural Complications	216 (49%)	20 (5%)	0	13 (6%)	4 (2%)	0
Abnormal Laboratory Tests	58 (13%)	19 (4%)	0	26 (13%)	7 (3%)	1 (<1%)
Metabolism and Nutrition Disorders	89 (20%)	12 (3%)	0	44 (21%)	6 (3%)	0
Musculoskeletal and Connective Tissue Disorders	98 (22%)	10 (4%)	0	44 (21%)	8 (4%)	0
Neoplasms (Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	5 (1%)	1 (<1%)	2 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
Nervous System Disorder	190 (43%)	83 (19%)	3 (1%)	75 (36%)	42 (20%)	0
Psychiatric Disorders	108 (25%)	16 (4%)	0	38 (18%)	6 (3%)	0
Renal and Urinary Disorders	42 (10%)	0	0	8 (4%)	2 (1%)	0
Reproductive System and Breast Disorders	8 (2%)	0	0	3 (1%)	0	0
Skin and Subcutaneous Tissue Disorders	104 (24%)	0	0	32 (15%)	1 (<1%)	0
Surgical and Medical Procedures	2 (<1%)	0	0	2 (1%)	0	0
Vascular Disorders	48 (11%)	16 (4%)	1 (<1%)	19 (9%)	10 (5%)	3 (1%)

Patients treated with Optune/TMZ experienced a small increase in TMZ-related AEs and SAEs due to the longer TMZ exposure afforded to these patients by their longer PFS. The only AEs which may have been caused by Optune therapy are the known skin irritation seen in 45% of patients in this study (1% severe) falls which were seen at a slightly higher incidence in patients carrying the device, headaches related to wearing the arrays 24 hours a day and mild psychiatric symptoms (anxiety, insomnia, confusion) which could be caused by the need to incorporate the device and arrays into daily life. No SAEs were considered related to device use. The remainder of AEs and SAEs seen in the trial were well balanced between treatment arms. In conclusion, Optune is very well tolerated with mild to moderate toxicity mainly related to array contact with the scalp.

Conclusions: Optune is a portable, battery operated device which delivers TFields to patients with recurrent diagnosed GBM. The results of the pivotal trial in newly diagnosed GBM showed that Optune/TMZ extends progression free and overall survival significantly compared to patients receiving TMZ alone. No significant increase in adverse events is seen when Optune treatment is added to TMZ. The only common device-related AE was a skin irritation seen beneath the transducer arrays in 45% percent of patients. The majority (14 of 45%) of these events were mild to moderate. Based on an assessment of the Quality of life of the interim analysis cohort of 315 patients, cognitive function and functional status did not decline due to the use of Optune/TMZ.

Pilot Clinical Study in Recurrent GBM

Optune has been tested in 10 recurrent GBM subjects in a single center, pilot study in Europe. In this study, Optune monotherapy led to a significant increase in time to progression (from 13 to 26 weeks; $p=0.013$), progression free survival at 6 months (PFS6) (from 15 to 50%) and overall survival (OS) (from 6.0 to 14.7 months; $p=0.002$) compared to matched concomitant and historical comparator groups. The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device transducer arrays.

Other Clinical Experience in Recurrent GBM

The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received Optune in a real-world, clinical practice setting in the US between 2011 and 2013. The registry included 457 recurrent GBM patients who received Optune in 91 US cancer centers. More patients in PRiDe than the pivotal clinical trial in recurrent GBM (EF-11) received Optune for first recurrence (33% vs. 9%) and had received prior bevacizumab therapy (55.1% vs. 19%). Median OS was significantly longer with Optune in clinical practice (PRiDe data set) than in the EF-11 pivotal trial in recurrent GBM (9.6 vs. 6.6 months). One- and 2-year OS rates were more than double for NovoTTF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% vs. 20%, 2-year: 30% vs. 9%). Favorable prognostic factors included first and second vs. third and subsequent recurrences, high Karnofsky Performance Score (KPS) and no prior bevacizumab use. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the Optune transducer arrays.

Pivotal Clinical Study in Recurrent GBM¹

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with Optune to those treated with an effective best standard of care (BSC) chemotherapy (including bevacizumab).

The following were the objectives of the study.

- To prospectively compare the median overall survival of recurrent GBM subjects treated with Optune to those treated with best standard of care (BSC) active chemotherapy
- To prospectively determine PFS6, TTF, 12-month survival and quality of life of subjects treated with Optune compared to BSC
- To collect evidence of the safety of TTFs applied to subjects with recurrent GBM using Optune.

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows.

Inclusion Criteria

- a. Pathological evidence of GBM using WHO classification criteria
- b. ≥ 18 years of age
- c. Not a candidate for further radiotherapy or additional resection of residual tumor
- d. Subjects with disease progression (by Macdonald criteria (i.e., $> 25\%$ or new lesion)) documented by CT or MRI within 4 weeks prior to enrollment
- e. Karnofsky scale ≥ 70
- f. Life expectancy at least 3 months
- g. Participants of childbearing age must use effective contraception
- h. All subjects must sign written informed consent

Exclusion Criteria

- a. Actively participating in another clinical treatment trial
- b. Within 4 weeks from surgery for recurrence
- c. Within 4 weeks from any prior chemotherapy
- d. Within 4 weeks from radiation therapy
- e. Pregnant
- f. Significant co-morbidities within 4 weeks prior to enrollment
 - 1) Significant liver function impairment (AST or ALT > 3 times the upper limit of normal)
 - 2) Total bilirubin $>$ upper limit of normal
 - 3) Significant renal impairment (serum creatinine > 1.7 mg/dL)
 - 4) Coagulopathy (as evidenced by PT or APTT > 1.5 times control in subjects not undergoing anticoagulation)
 - 5) Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
 - 6) Neutropenia (absolute neutrophil count $< 1 \times 10^3/\mu\text{L}$)
 - 7) Anemia (Hb < 10 g/L)
 - 8) Severe acute infection
- g. Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias
- h. Intra-tentorial tumor
- i. Evidence of increased intracranial pressure (midline shift > 5 mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

Study Procedures:

Treatment Arm

At treatment initiation subjects were hospitalized for 24 hours. During this period baseline examinations were performed and Optune treatment was initiated by the investigator under continuous medical supervision. The subjects were also instructed by the investigator on the operation of Optune and battery replacement. Once the subjects were trained in operating the device they were released to continue treatment at home. The subjects received continuous Optune treatment. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Subjects received the best effective standard of care chemotherapy practiced at each of the participating centers. The effective BSC treatments used in the study were comprised mainly of the following chemotherapies: Platinum based chemotherapy (Carboplatin), Nitrosureas (BCNU), Procarbazine, lomustine and vincristine (PCV), TMZ, Bevacizumab, and Imatinib, erlotinib, irinotecan (mainly in Europe). Because these therapies were included in the trial as a group, no comparisons can be made to each individual chemotherapy regimen. Chemotherapeutic treatment protocol was according to standard procedures at each of the participating centers.

Follow-up

During treatment, and until progression for subjects who stopped treatment before progression, all subjects were seen once a month at an outpatient clinic where they underwent medical follow up and routine laboratory exams. An MRI was performed every 2 months until disease progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each subject. Medical follow-up continued for 2 months following disease progression. Subject survival was assessed based on monthly telephone interviews with the subjects' caregivers.

Subject Characteristics: 237 subjects (120 Optune, 117 BSC) with progressive or recurrent GBM were enrolled in the study. Baseline characteristics were as follows: mean age 53.6 years; mean Karnofsky score: 81.6±10.9%, tumor size (cm³): 16.2±12.4; progression number: 1.4±0.9; re-operated: 26%; male: 70%; previous low grade: 10%; prior bevacizumab failure: 19%. Baseline characteristics were similar between treatment groups with slightly more men in the Optune group than in the BSC group (77% vs. 62%), a lower incidence of frontal lobe tumors in the Optune group than in the BSC group (32% vs. 50%), and a slightly higher mean KPS in the Optune group than in the BSC group (83% vs. 80%), though the median KPS was 80 in both groups. Adjusted analyses for all pre-specified or all statistically significant baseline covariates for overall survival did not change the outcome of the trial.

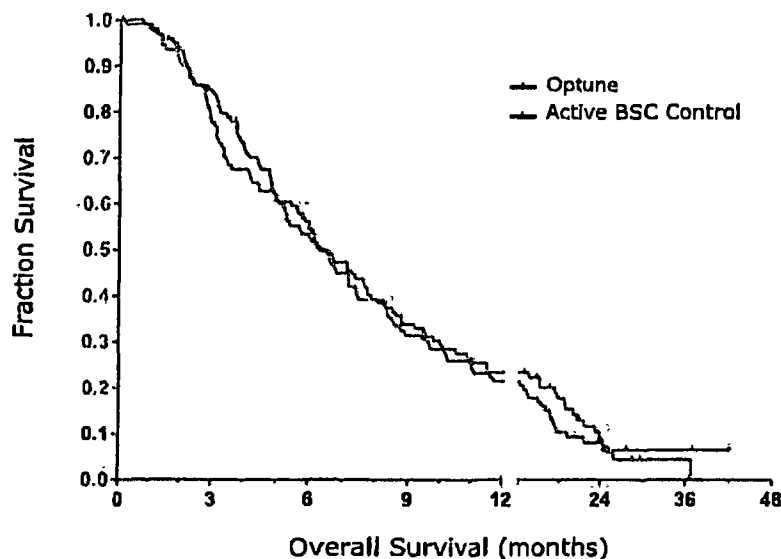
Demographics and Baseline Characteristics (ITT)		
	Optune	BSC
Characteristics	(N=120)	(N=117)
	n (%)	n (%)
Caucasian	111 (93)	106 (91)
African American	2 (2)	5 (4)
Asian	0	3 (3)
Hispanic	7 (6)	2 (2)
Other	0	1 (1)
Female Gender	28 (23)	44 (38)
Frontal Tumor Position	38 (32)	58 (50)
Bilateral or Midline Tumor Location	23 (19)	17 (15)
Prior Avastin Use	24 (20)	21 (18)
Re-operation for Recurrence	33 (28)	29 (25)
Prior Low-grade Glioma	12 (10)	11 (9)
Median Age (years) (min, max)	54 (24, 80)	54 (29, 74)
Median Weight (kg)	80	80
Mean Number of Prior GBM Recurrences	1.5	1.3
Median Karnofsky Performance Score (min, max)	88 (50, 100)	80 (50, 100)
Median Tumor Area (mm ²)	1440	1391
Median Time from GBM Diagnosis to Randomization (days)	334	340
Mean Time from Last Radiotherapy Dose to Randomization (Months)	13.71	13.93

Effectiveness Results:**Primary Effectiveness Endpoint: Overall Survival (ITT)**

In the ITT population which included all randomized subjects (Novo-ITF=120, BSC=117), overall survival in subjects treated with Optune was comparable to that observed in subjects treated with BSC (median OS=6.3 vs. 6.4 months; $p=0.98$). In the US, the median overall survival was 6.1 vs. 5.3 months in the ITT population. The pivotal study data establish that Optune therapy is comparable to BSC therapy in extending OS.

	Treatment Group	
	Optune	BSC
N	120	117
Median OS (months)	6.3	6.4
Log-rank p-Value	0.98	
Hazard Ratio (95% CI)	1.00 (0.76-1.32)	

The Kaplan-Meier survival curve for the two treatment groups appeared to be very similar during the first 12 months of follow-up, where 80% of the events occurred in both groups. Between 12 and 24 months, the survival curves separated slightly in favor of the BSC control group. However, after 12 months, the number of subjects remaining may be too small to reliably estimate the long term survival outcome.



	Optune (N=120)	Active BSC Control (N=117)
Deaths	105	97
Censored	15	20
Lost to follow-up	6	10
Alive at end of follow-up	9	10
Median (months)	6.3	6.4
95% Confidence Interval	5.6, 7.8	5.2, 7.4

Correlation between Treatment Compliance and Overall Survival: Optune has an internal log file which allows the calculation of patient compliance with treatment. Significantly higher overall survival ($p=0.0447$) was observed in patients who were treated 75% or more of the time on average (OS=7.7 months) compared to patients treated less than 75% of the time on average (OS=4.5 months).

Secondary Effectiveness Endpoints: Secondary endpoint results support the findings in the primary endpoint. The one-year survival is similar in the Optune and BSC groups in the ITT population (21.9% vs. 22.1%). Progression free survival at 6 months (PFS6) is the same in the ITT population (21.4% vs. 15.2%). Radiological response rates from the subset of patients evaluated were reported as 14% for the Optune group compared to 9.6% for the BSC group in the ITT population. Median time to progression (TTP) was 9.3 weeks for Optune vs. 9.6 weeks for BSC.

	Treatment Group	
	Optune	BSC
N	120	117
1-year survival	21.9% 25/114	22.1% 23/104
PFS6 (%)	21.4% 22/103	15.2% 14/92
Radiological Response Rate (%)	14.0% 14/100	9.6% 7/73
Median TTP (weeks)	9.3	9.6

Quality of Life: Quality of life in subjects using Optune was better than those on BSC chemotherapy in most subscale domains, including vomiting, nausea, pain, diarrhea, constipation, cognitive and emotional functioning.

Safety Results: The characteristic adverse events of almost all chemotherapies are seen in a significantly higher proportion of BSC control subjects than in Optune subjects: gastrointestinal (30% vs. 8%), hematological (19% vs. 4%) and infectious (12% vs. 4%). Mild to moderate skin irritation beneath the device transducer arrays was observed in 16% of Optune subjects; none of these cases were assessed as severe by the investigator, all resolved after discontinuing treatment, and all were treated with topical steroids and periodic shifting of transducer array positions.

Number of Patients with Adverse Events by Body System (>2%)

System Organ Class	Optune	BSC Chemotherapy
	N=116 (%)	N=91 (%)
Blood and lymphatic disorders	5 (4.3%)	17 (18.7%)
Gastrointestinal disorders	9 (7.8%)	27 (29.7%)
General disorders and administration site conditions	15 (12.9%)	14 (15.4%)
Infections and infestations	5 (4.3%)	11 (12.1%)
Injury, poisoning and procedural complications	21 (18.1%)	1 (1.1%)
Metabolism and nutrition disorders	9 (7.8%)	12 (13.2%)
Nervous system disorders	50 (43.1%)	33 (36.3%)
Psychiatric disorders	12 (10.3%)	7 (7.7%)
Respiratory, thoracic and mediastinal disorders	7 (6.0%)	10 (11.0%)

Conclusions: Optune is a portable, battery operated device which delivers TTFields to patients with recurrent GBM. The results of the pivotal trial showed that Optune subjects had comparable overall survival to subjects receiving the best available chemotherapy in the US today (OS 6.3 vs. 6.4 months; HR 1.0; p=0.98). Similar results showing comparability of Optune to BSC chemotherapy in the ITT population were seen in all secondary endpoints.

Optune subjects experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to BSC controls. The only device-related adverse event seen was a mild to moderate skin irritation beneath the device transducer arrays, which was easily treated with topical ointments. Finally, certain quality of life measures were better in Optune subjects as a group when compared to subjects receiving effective BSC chemotherapy.

Directions for Use

Detailed directions for use for Optune can be found in:
The Optune Patient Information and Operation Manual

Abbreviations

AE – Adverse event

BSC – Best standard of care (effective chemotherapies)

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor

ITT – Intent-to-Treat. This analysis population includes all randomized subjects.

kHz – kilo hertz; number of cycles per second

Optune– A portable battery, or power supply, operated device for delivering 200 kHz TTFields to the brain of patients with recurrent GBM

OS – Overall survival

PP – Per Protocol. This analysis population includes all patients who received at least the first course of TMZ and had no major protocol deviations.

PFS – Progression free survival

PFS6 – Proportion of patients alive and progression free at 6 months from randomization

Radiological Response Rate – sum of complete and partial radiological response rates

TMZ – a type of cancer drug used to treat newly diagnosed GBM

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body afflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

TTP – Time to progression

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

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A multidisciplinary organization for the advancement of neuro-oncology through research and education

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The following abstract will be presented on Saturday, November 15, 2014, at 11:40am at the 19th Annual Scientific Meeting of the Society for Neuro-Oncology. The information below is embargoed until 8:00am, Saturday, November 15, 2014.

Interim Analysis of the EF-14 Trial: A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM

Roger Stupp, Eric Wong, Charles Scott, Sophie Taillibert, Andrew Kanner, Santash Kesari and Zul Ram on behalf of the EF-14 Trial investigators

BACKGROUND: Tumor Treating Fields (TTFields) are an anti-mitotic, physical treatment modality that acts in metaphase, anaphase and telophase. The NovoTTF-100A System (NovoTTF), a home-use medical device that delivers TTFields to the brain, is an established monotherapy for recurrent glioblastoma (GBM).

METHODS: We conducted an international, multicenter, prospective, randomized phase III trial in newly diagnosed GBM patients. After completion of radiotherapy (RT) with concomitant temozolomide (TMZ), patients were randomized (2:1) to adjuvant TMZ with NovoTTF or adjuvant TMZ alone. The primary endpoint was progression-free survival (PFS), with overall survival (OS) an important secondary endpoint. Here we report on a pre-specified interim analysis of the first 315 patients randomized, after a minimum follow-up of 18 months (range 18-60 months).

RESULTS: (intent-to-treat): 210 pts were randomized to NovoTTF/TMZ and 105 to TMZ alone. Patient characteristics were balanced: median age 57 and 58 years, tumor resection in 89 and 90%, KPS 90%, for the NovoTTF and the control arms, respectively. MGMT promoter methylation status was assessable centrally in 60% of patients; of these 39% and 41% were methylated. Adverse events (AE) were comparable between treatment arms. The most common device-related AE was skin irritation in 45% of patients (all grades, severe 2%). Severe seizures were observed at a frequency of 7% in both arms. Median PFS was 7.1 months (mo) (95% confidence interval [CI] 5.9-8.2) and 4.0 mo (CI 3.0-4.3; Hazard ratio 0.63, p=0.001), OS was 19.6 mo (CI 16.5-24.1) and 16.6 mo (CI 13.5-19.1) (HR 0.75, p=0.034), both favoring NovoTTF. This translates into a 24-mo survival rate of 43% (CI 36-50%) and 29% (CI 21-39%) for the NovoTTF/TMZ and the TMZ alone arm, respectively.

CONCLUSIONS: The trial met its primary and main secondary endpoints, and was closed to accrual after this interim analysis. Adjuvant TMZ chemotherapy and NovoTTF provides a clinically and statistically significant improvement in progression-free and overall survival, and should become the new standard of care against GBM.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C5-08-27
Baltimore, Maryland 21244-1850



Center for Medicare

Refer to: FCHBE

JUL 26 2013

James C. Stansel
Sidley Austin LLP
1501 K Street, NW
Washington, DC 20005

Dear Mr. Stansel:

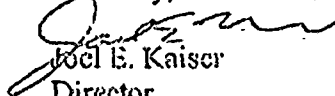
Thank you for your inquiry requesting an informal benefit category determination (BCD) for the NovoTTFTM-100A System.

According to your letter and the information you provided during the meeting with Centers for Medicare and Medicaid Services (CMS) on May 21, 2013, the NovoTTFTM-100A System is a non-invasive system used in the patient's home that delivers tumor treating fields therapy to the brain to disrupt rapid cell division exhibited by recurrent GBM tumors. The NovoTTFTM-100A System is comprised of a durable electrical field generator and disposable insulated transducer arrays for use with the Generator. The System also includes lithium ion batteries, battery rack, battery charger, power supply, connection cables, and a carrying case. The NovoTTFTM-100A System received pre-market approval (PMA) from FDA in April 2011 for recurrent GBM.

In order for an item to be covered by Medicare, it must meet the definition of a Medicare-covered benefit. However, it is important to note that although Medicare provides coverage for certain items, it does not provide coverage for every item that may be useful to a person with a medical problem, even if a physician prescribes the item. The Medicare definition of durable medical equipment (DME) includes equipment which: can withstand repeated use; has an expected life of at least three years; is primarily and customarily used to serve a medical purpose; generally is not useful to a person in the absence of an illness or injury; and is appropriate for use in the home.

Based on the product information we reviewed, we believe that the NovoTTFTM-100A System falls within the DME benefit category. I hope that this information is helpful to you.

Sincerely,


Joel E. Kaiser
Director
Division of DMEPOS Policy

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OPTUNE™
(FORMERLY NOVOTTF™-100A SYSTEM)

CLINICAL DOSSIER

TUMOR TREATING FIELDS THERAPY

Treatment for Glioblastoma Multiforme

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List of Abbreviations and Definitions of Terms

AE – Adverse Event

BCNU – Carmustine, chemotherapy

BPC – Best Physician Choice

BSC – Best Standard Care

c – Centigrade

CCNU – Lomustine (CeeNU), chemotherapy

CE Mark -- Conformité Européene mark, for products sold in the European Economic Area

CI – Confidence Interval

cm – Centimeters

DTIC -- Dacarbazine

dAEs -- Dermatologic adverse events

ECG -- Electrocardiogram

EMC -- Electromagnetic Compatibility

F-98 – Rat glioblastoma cell line

FDA -- Food and Drug Administration

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor

Gy – Gray, unit of radiation

HR -- Hazard Ratio

ITT – Intent-to-Treat

INE – Insulated Electrical Array

kHz – Kilo Hertz; number of cycles per second

KPS – Karnofsky Scale

mHz -- Mega Hertz, number of cycles per second

MGMT -- 06-methylguanine-DNA methyltransferase

MITT -- Modified intention-to-treat

mo. -- Months

MRI -- Magnetic Resonance Imaging

ORR - Objective Response Rate

OS – Overall Survival

PCV – Procarbazine, CCNU and vincristine-combination chemotherapy

PFS – Progression Free Survival

PFS6 – Progression Free Survival at 6 months

PMA – Pre-market Approval

PRiDe -- Patient Registry Dataset

QOL – Quality of Life

RR – Radiological Response Rate--Sum of complete and partial radiological response rates

TENS -- Transcutaneous Electrical Nerve Stimulation

TMZ--Temozolomide

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body afflicted with a solid tumor. The fields have been shown to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase.

U-87 - Human glioblastoma cell line

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US – United States

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

WHO -- World Health Organization

This diagram shows the components of a portable electronic device, likely a radio or communication unit, arranged in an exploded view. The components are numbered 1 through 7:

- 1:** A rectangular power supply or battery pack with a cable and a connector.
- 2:** A base unit or chassis with a perforated front panel and internal components.
- 3:** A small, flat rectangular component, possibly a filter or capacitor.
- 4:** A large, dark, rectangular component, possibly a speaker or a large capacitor.
- 5:** A small, cylindrical component, possibly a resistor or a small capacitor.
- 6:** A coiled cable or hose, possibly for ventilation or a connection.
- 7:** A small, rectangular component, possibly a switch or a small module.

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Figure 2. Use of Device Overview



1. Prepare scalp.



2. Remove four transducer arrays from package.



3. Place transducer arrays on scalp.



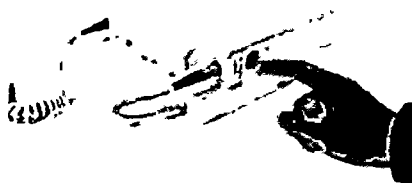
4. Connect transducer arrays to connection cable & device. Match colored rings to color coded sockets.



5. Place device and battery in bag (if applicable) and connect battery or power supply.



6. Connect connection cable to device.



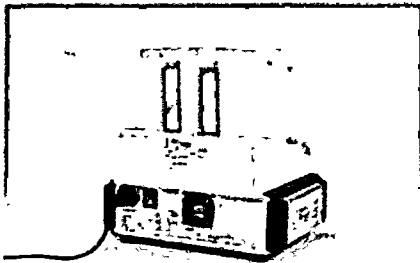
7. Start treatment. Turn on power switch and push TTFields button.



8. Place bag over shoulder.



9. Replace transducer arrays as needed.



10. Recharge batteries when not in use.

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1] Burden of Illness and Standard of Care for GBM

Glioblastoma multiforme (GBM), a malignant form of astrocytoma, is the most common and most aggressive form of primary brain cancer; but it remains a rare disease.

Burden of Illness

The incidence of GBM increases steadily above 45 years of age, with approximately 10,000 new cases annually in the United States. GBM tends to occur more frequently in males than females by a ratio of about 3:2. The outcome of patients with this disease has not improved significantly in recent years, despite the introduction of improved chemotherapies, including temozolomide (TMZ) (Merck; Temodar), bevacizumab (Roche, Avastin), and the use of GLIADEL® Wafers (carmustine). The 4-year survival of these patients is only 6.3% with a median overall survival (OS) of 14.6 months (Ostrom, 2015).

Nearly all patients with newly diagnosed GBM relapse within the first year despite aggressive treatment. Recurrent GBM is an end-stage condition; median OS from time of recurrence is approximately 3 to 5 months without additional effective treatment.

Quality of Life (QOL) for patients with GBM is generally poor due to the neurological deficits caused by the tumor itself together with the associated side effects of the various approved and experimental treatments.

Insurance Burden

To determine which US health insurers cover GBM patients, it is helpful to know that the median age at diagnosis is approximately 64 years. Therefore, the expected population for a private health care payer in the US is approximately 16 patients per 1 million covered lives (10,000 with GBM x 50% non-Medicare x 64% with private health care coverage = 3,200 divided by 201.1 million covered lives with private insurance = 16 lives per million covered).

Existing Treatment Options for GBM

There are currently four principal treatment options for GBM. Even with these treatments, the median time to recurrence of the tumor has been extended by only a few months. Once the tumor has recurred, patients have limited treatment options.

Newly Diagnosed GBM

Standard of care for a patient with newly diagnosed GBM and adequate functional status is debulking surgery, radiation with concurrent TMZ followed by adjuvant TMZ. Some elderly patients simply receive standard radiation or TMZ. Any or all of the following options may be pursued:

- **Surgical Resection** – Surgery to debulk the tumor and obtain tissue for diagnosis is the most common initial approach for newly diagnosed GBM. The surgical goal is to remove as much of the tumor as possible without

compromising neurological function. When surgical resection is not feasible due to tumor location or patient's clinical condition, open or stereotactic biopsy may be performed.

- **GLIADEL® Wafer in Combination with Surgical Resection** – The GLIADEL® Wafer may be placed in the brain cavity at the time of surgical resection to deliver carmustine (BCNU) directly to the site of the brain tumor (interstitial chemotherapy). A modest increase in median survival has been shown over placebo (13.9 mo. vs. 11.6 mo.) when used in newly diagnosed GBM. Treatment with GLIADEL® wafer is associated with the following common side effects (incidence >10% and between arm difference ≥4%): cerebral edema, asthenia, nausea, vomiting, constipation, wound healing abnormalities and depression.
- **Radiation Therapy – Localized radiotherapy is typically given over a six-week period following surgical resection with a total dose of approximately 60 grays (Gy).** Side effects of radiation therapy depend on the type of radiation received, the amount of the surface of the brain targeted, the site targeted, and the total dose of radiation. In general, there will be hair loss, skin irritation, possible hearing problems, nausea, vomiting, loss of appetite, and neurologic effects. The most prevalent side effect is fatigue, which may last through treatment and for many months afterwards.
- **Cytotoxic Chemotherapy** – TMZ, an oral alkylating agent, is administered concomitant with radiation therapy and continued for a minimum of six months following radiation. Significantly improved OS and median survival have been demonstrated in large trials. Recent studies have shown that patients with methylated O6-methylguanine-DNA methyltransferase (MGMT) may have a superior response to TMZ therapy. Side effects from TMZ therapy include: nausea, vomiting, loss of appetite, constipation, tiredness, and headache. Temporary loss of hair also can be expected.

Recurrent GBM

There is little data on effective strategies for treatment of recurrent GBM.

- **Surgical Resection** – Repeat surgery for GBM at the time of tumor recurrence may be offered when it is feasible although there is no data indicating that it offers significant survival benefit. Second surgery is considered in only about 20% of patients.
- **GLIADEL® Wafer in Combination with Surgical Resection** – Use of GLIADEL® Wafer is limited to selected cases undergoing additional surgical resection for recurrent GBM. The package insert indicates that for recurrent GBM, GLIADEL® Wafer increased median OS from 4.6 to 6.5 months compared to placebo.

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- **Radiation Therapy** - Because the full standard dose of radiation (60 Gy) typically is given after initial diagnosis with GBM, irradiation for disease recurrence may not be possible. However, with advances in technology, re-irradiation with fractionated stereotactic radiotherapy can provide survival benefit.
- **Cytotoxic Chemotherapy** - There is no established standard treatment for recurrent GBM. Chemotherapy treatment strategies are ill-defined, with several different preferred regimens. The most common are: nitrosureas, (BCNU), procarbazine, PCV (procarbazine, CCNU and vincristine), and platinum based (e.g. carboplatin). None of these agents is FDA approved specifically for recurrent GBM. Most patients suffer from combinations of unpleasant and sometimes life-threatening side effects of their chemotherapeutic treatments,
- **Bevacizumab (Avastin)** may be used as monotherapy for patients with recurrent GBM (Cohen, 2009). The FDA approval was based on two phase 2, single arm trials comparing bevacizumab to historical control data. Benefit was seen in objective response (OR) rates and progression free survival at six month (PFS6) compared to historical control data. OS was shown to be between 8 to 9 months however, an OS claim is not made in the approved labeling

In summary, despite an aggressive initial standard of therapy treatment, most GBM patients develop recurrent disease. When tumors recur, only 20% of patients are eligible for additional resection. There is a high unmet need for therapies to treat recurrent GBM.

2] Description and Use of Optune

Overview

Optune is a portable, wearable medical device, which produces alternating electrical fields, tumor treating fields or "TTFields," within the brain by means of electrically-insulated surface transducer arrays placed on the scalp. The TTFields are believed to disrupt the rapid cell division exhibited by cancer cells.

Indication for Use:

Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme. (GBM)

Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy

For the treatment of recurrent GBM, Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supratentorial region of the brain after

receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options

Summary of Important Safety Information:

Contraindications

Do not use Optune if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement), or bullet fragments. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune if you are known to be sensitive to conductive hydrogels. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions

Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by Novocure (the device manufacturer).

Do not use Optune if you are pregnant, you think you might be pregnant or are trying to get pregnant. It is not known if Optune is safe or effective in these populations.

The most common ($\geq 10\%$) adverse events involving Optune in combination with temozolomide were low blood platelet count, nausea, constipation, vomiting, fatigue, scalp irritation from device use, headache, convulsions, and depression.

The most common ($\geq 10\%$) adverse events seen when using Optune alone were scalp irritation from device use and headache.

The following adverse reactions were considered related to Optune when using the device alone: scalp irritation from device use, headache, malaise, muscle twitching, fall and skin ulcer.

All servicing procedures must be performed by qualified and trained personnel.

Do not use any parts that do not come with the Optune Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor.

Do not wet the device or transducer arrays.

If you have an underlying serious skin condition on the scalp, discuss with your doctor whether this may prevent or temporarily interfere with Optune treatment.

Treatment Start

Treatment initiation often takes place in the patient home. The patient and caregiver receive device related training from a Novocure representative. The patient has his or her scalp shaved to ensure proper contact of the transducer arrays to the skin. The caregiver places the arrays in accordance with the prescribed array layout and initiates therapy by turning the device on. (See **Figure 2** for illustration.)

Patient and Caregiver Training

Novocure representatives are responsible for training the patient and caregiver on the technical aspects and use of the device. All medical questions are referred back to patient's provider. This training involves technical training related to the device operation, including educating the patient on battery replacement, battery charging, using the power supply, connecting and disconnecting from the device, and on the appropriate placement of transducer arrays in accordance with the treatment plan. Additionally, the patient and caregiver will have access to a 24-hour technical support service offered by the device manufacturer.

Transducer Array Placements – After Successful Patient Training

The patient and caregiver, once properly trained, are expected to change the transducer arrays. The caregiver will be trained to shave the patient's scalp, maintain good skin care protocols, and to place the arrays in accordance with the prescribed treatment plan. The arrays are changed and the scalp is re-shaved about every three to four days to ensure contact with the skin. Patients know to change the arrays when the alarm beeps more often to signal the need for the change.

Monthly Treatment Assessment

Patients typically are scheduled to meet the physician once per month, exclusive of Optune treatment. The Novocure Representative will provide the physician a monthly compliance report which is reviewed with the patient during this appointment. The compliance log provides the physician with an overview of device usage by day and by time of day (day versus night). The physician uses this compliance log to encourage appropriate use of Optune. During this monthly appointment, the physician also reviews transducer array location to ensure appropriate placement in accordance with the prescribed treatment plan. If compliance is problematic, patients and caregivers may be retrained in the proper use of the device.

Device Use Overview

Treatment Duration

The physician-prescribed device is used for newly diagnosed patients in combination with temozolomide and as monotherapy for patients diagnosed with recurrent glioblastoma. Physicians may choose to keep patients on Optune at first recurrence. For maximum benefit, the recommended average daily use is at least 18 hours a day.

Device Settings

Novocure pre-sets all device treatment parameters; there are no programming adjustments available to the patient. The patient simply connects the device to an

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appropriate power supply (i.e., a charged battery or connection of the power supply to an electrical outlet) and turns it on and off.

Practical Considerations

Treatment may be interrupted for personal needs such as bathing or exercise. In order to take a shower, the patient must disconnect from the device (leaving the transducer arrays on the head), put on a shower cap, and be cautious not to get his/her head or any components of the device wet. Treatment also must be stopped to replace the arrays. When leaving the house, patients can put a wig or hat over the arrays, if desired.

Device Service

The device and batteries require frequent servicing. Novocure provides the patient with replacements for these components, as needed, and in most cases ships on an overnight basis. For minor technical issues, an alarm will sound to notify the patient. The patient manual has a simple troubleshooting guide that addresses the most common problems that may arise. In addition, Novocure has around-the-clock technical support. Patients are encouraged to call the Novocure technical support telephone number with questions about operations or device function.

FDA Approvals

The US Food and Drug Administration (FDA) approved Optune for use in newly diagnosed GBM in October 2015. (See FDA Approval Letter, **Appendix A.**)

Optune has been available for use in recurrent GBM since FDA approval (via premarket approval (PMA) pathway) in April 2011. (See FDA Approval Letter, **Appendix A.**)

Regulatory Approval Outside the United States

Optune is a CE Marked (Conformité Européene) device cleared for sale in the European Union, Switzerland, Australia, Israel and Japan.

3] Optune Mechanism of Action

Background

The Optune System delivers tumor treating fields (TTFields) to the tumor. TTFields are intended to disrupt cancer cell division by utilizing the unique electrical and geometric properties of cells during the mitotic process.

Electric fields traditionally have been used in medicine in two different modes: 1) steady or low frequency electric fields (<1 kHz); and 2) high frequency alternating fields (>10 mHz). Steady or low frequency electric fields generate action potentials in excitable cells. These fields are used therapeutically in bone and soft tissue repair, pain control (TENS), and stimulation (neurologic or cardiac). In contrast, very high frequency

alternating fields generate heat in the tissues by dielectric losses. Applications in therapeutic use include ablation, diathermy and hyperthermia.

In contrast, Optune harnesses intermediate frequency (200 kHz), low intensity (1-3 V/cm), alternating electric fields) to achieve its therapeutic effect. At this frequency and intensity, Optune cannot stimulate nerves or muscles or bone growth, nor do they heat the tumor or surrounding tissues. Since Optune is applied using electrically insulated arrays, there is no direct current flow into the tissue hence electrolysis and tissue damage do not occur. TTFIELDS are delivered non-invasively via the arrays to GBM tumors using the Optune device.

Mechanism of Action

TTFIELDS target two specific characteristics of cancer cells: the presence of electrically charged particles during mitosis and the geometrical shape of dividing cancer cells. TTFIELDS have been shown to:

- inhibit cancer cell replication by interference with the proper formation of the mitotic spindle during metaphase and anaphase; and
- cause intracellular dielectrophoresis of macromolecule and organelles during cytokinesis.

Acting together, these two processes, which are specific to dividing cells only, may lead to apoptosis and can result in tumor arrest or regression *in vivo*.

In contrast, data indicate that Optune does not affect cells that are quiescent, that is, that are not dividing. Since most normal adult brain cells proliferate very slowly, if at all, scientists hypothesize that these cells are affected minimally by Optune. Additionally, the antimitotic effect of Optune has been shown to be frequency-specific to the cell type treated.

Optune application has the advantage of being locally-directed and is not expected to be associated with systemic toxicity.

4] Summary of Clinical Studies

Pilot and pivotal studies in both newly diagnosed and recurrent GBM have demonstrated that Optune is safe and effective in patients with GBM. The most recently completed study, EF-14 in newly diagnosed GBM, compared Optune in combination with maintenance TMZ compared to TMZ alone. The previous EF-11 trial for recurrent GBM compared Optune alone with best physician choice chemotherapy (BPC). To date, Optune therapy has been used in more than 2500 patients in the clinical as well as commercial setting. What follows is a synopsis of the EF-14 pivotal trial in newly

Exclusion Criteria

- *Progressive disease (according to MacDonald Criteria¹).*
- *Actively participating in another clinical treatment trial*
- *Pregnant*
- *Significant co-morbidities at baseline which would prevent maintenance TMZ treatment:*
 - *Thrombocytopenia (platelet count < 100 x 10³/μL)*
 - *Neutropenia (absolute neutrophil count < 1.5 x 10³/μL)*
 - *CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)*
 - *Significant liver function impairment - AST or ALT > 3 times the upper limit of normal*
 - *Total bilirubin > upper limit of normal*
 - *Significant renal impairment (serum creatinine > 1.7 mg/dL)*
- *Implanted pacemaker, defibrillator, deep brain stimulator, or documented clinically significant arrhythmia.*
- *Infra-tentorial tumor*
- *Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)*
- *History of hypersensitivity reaction to TMZ or a history of hypersensitivity to dacarbazine (DTIC).*

Study Procedure After completion of treatment with TMZ and radiotherapy, patients were randomized at a ratio of 2:1 to receive standard maintenance TMZ (150-200 mg/m²/d for 5 days every 28 days for 6-12 cycles) with or without the addition of Optune. The web-based randomization was stratified by extent of resection and MGMT methylation status.

Treatment Arm: Optune was given together with maintenance TMZ. At treatment initiation, patients were seen at an outpatient clinic. During this visit, patients received baseline examinations and Optune treatment was initiated. The patients were instructed on the operation of Optune and battery replacement. Once the patients were trained in operating the device, they were released to continue treatment at home. Following radiological progression or unacceptable toxicity, TMZ could be replaced with BSC second line chemotherapy. However, Optune could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

¹ The Macdonald criteria divides response into 4 types of response based on imaging (MRI) and clinical features: complete response; partial response; stable disease; progression.

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Control Arm: All subjects had baseline examinations performed prior to treatment initiation. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with BSC second line therapy.

Follow Up: During treatment, all patients were seen once every month at an outpatient clinic where they underwent medical follow-up and routine laboratory exams. Treatment adherence with Optune was recorded by the device, then reviewed and transferred at follow-up visits. A magnetic resonance imaging (MRI) was performed every second month following the baseline MRI until second progression or 24 months (whichever came first), when treatment on both arms of the study was terminated. In the case of clinical progression, an unscheduled MRI was obtained within 1 week after the investigator became aware of the clinical progression. No additional MRIs were required after second progression. Central MRI review was performed by an independent radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality was assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Study Patients: The study enrolled 695 of the 700 planned patients between July 2009 and November 2014; Optune/TMZ (n = 466) or TMZ alone (n = 229). Data from the prespecified interim analysis of the first 315 patients with a minimum of 18 months of follow-up included 210 patients in the Optune plus TMZ arm and 105 in the TMZ alone arm. Baseline characteristics were well balanced in both groups. (See Appendix B) An independent data and safety monitoring committee review of the interim data determined that the predefined improvement in PFS and OS had been met and recommended termination of the study. Following FDA approval of the termination, the study was closed to recruitment and patients in the control group were allowed to crossover and receive Optune. A total of 35 patients crossed over. Follow-up for all patients continues; final analysis data are not expected before the end of 2016. The results that follow here are from the interim analysis.

Analysis Populations: PFS was analyzed in the intent-to-treat (ITT) population, which included all randomized subjects (Optune/TMZ--210; TMZ alone--105 at the interim analysis). OS was analyzed in the PP population which excluded all patients who 1) never started TMZ maintenance therapy, 2) had major protocol violations, 3) crossed over to the other treatment group, or 4) received Optune outside the protocol (Optune/TMZ=196; TMZ alone=84).

Treatment Delivery

The median number of TMZ cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the Optune plus TMZ arm and 4 cycles (range, 1-24 months) in the TMZ arm alone. The median duration of treatment with Optune was 9 months (range, 1-58 months). Two-thirds of patients in the Optune plus TMZ arm continued treatment with TTFIELDS after first tumor progression. Three-quarters of

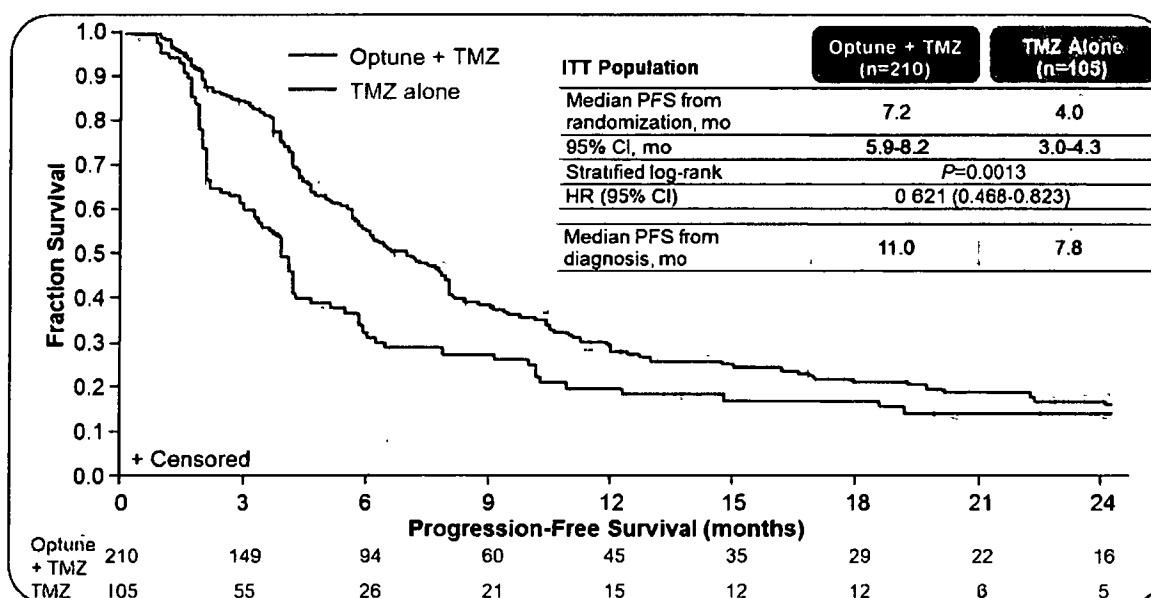
patients receiving Optune complied with therapy, wearing the device >18 hours per day on average for the first 3 treatment months.

Effectiveness Results:

Primary Effectiveness Endpoint: Progression Free Survival--ITT Population

The threshold for statistical significance of PFS at the interim analysis was pre-defined as an α level of .01 using a stratified log-rank test. PFS at the interim analysis met this threshold. After a median follow-up of 38 months (range, 18-60 months), the median PFS from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the Optune plus TMZ arm compared with 4.0 months (95% CI, 3.3-5.2 months) in the TMZ only arm. Thus, the addition, of Optune to BSC TMZ extended median PFS by 3.1 months. (See Figure 3.)

Figure 3. Progression Free Survival: ITT Population



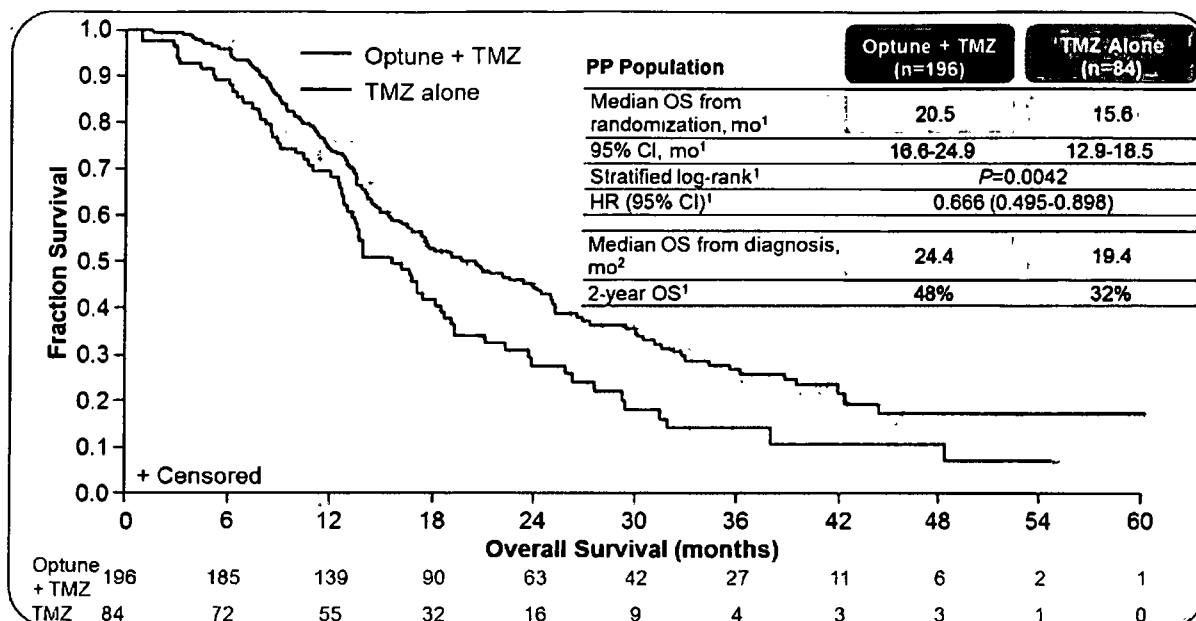
Secondary Effectiveness Endpoint: Overall Survival--PP population

OS was a powered secondary analysis in the trial and was to be tested only after the primary endpoint was found to surpass the threshold for significance in the interim analysis. The threshold for superior OS at the interim analysis was predefined in the protocol as an α level of .006 using a stratified log-rank test and was to be tested in the PP population (Optune/ TMZ = 196, TMZ alone = 84). Median OS in the PP population was 20.5 months (95%CI, 16.7-25.0 months) in the Optune plus TMZ arm compared with 15.6 months (95%CI, 13.3-19.1 months) in the TMZ alone arm.

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Figure 4. Overall Survival: PP Population



In an additional survival analysis of the ITT population, median OS was 19.6 months (95% CI, 16.6-24.4 months) in the Optune plus TMZ arm compared with 16.6 months (95% CI, 13.6-19.2 months) in the TMZ alone arm. Further, the percentage of patients alive at 2 years following enrollment was 43% in the Optune plus TMZ arm compared with 29% in the TMZ alone arm.

Robustness Analysis: To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Baseline characteristics of all patients randomized were similar to the interim data set as were the results for the main endpoints. PFS in the ITT population was 7.1 months (95% CI, 6.1-8.13 months) for the Optune plus TMZ arm and 4.2 months (95% CI, 3.93-5.87 months) for the TMZ alone arm. OS in the ITT population also favored Optune treated patients with a median of 19.4 months (95% CI, 16.6-23.9 months) vs. 16.6 months (95% CI, 13.9-18.6 months).

Safety Results: The addition of Optune to TMZ in patients with newly diagnosed GBM was not associated with any significant increase in systemic toxic effects compared with TMZ alone. (See **Appendix C**) However, patients receiving Optune did experience a higher incidence of localized skin toxicity (medical device reaction beneath the transducer arrays). Mild to moderate skin irritation was observed in 43% of patients treated with Optune plus TMZ and severe skin reaction (grade 3) noted in 2%. Skin reactions could be managed by using published skin care guidelines for patients receiving Optune. Mild anxiety, confusion, insomnia and headaches were reported more frequently in patients treated with Optune plus TMZ and occurred mainly at the time of therapy initiation. The incidence of seizures was 7% for the Optune plus TMZ arm and

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8% in the TMZ alone arm. Twelve patients died of causes considered to be unrelated to treatment, 8 (3.9%) in the Optune plus TMZ arm and 4 (4.0%) in the TMZ alone arm.

Conclusions: Results of the interim analysis of the pivotal trial in newly diagnosed GBM show that Optune plus TMZ significantly extends PFS and OS compared to patients receiving TMZ alone. The addition of Optune to BSC TMZ was shown to be safe; no significant increase in serious AEs was seen when Optune treatment was added to TMZ. The most common ($\geq 10\%$) adverse events involving Optune in combination with TMZ were low blood platelet count, nausea, constipation, vomiting, fatigue, scalp irritation from device use, headache, convulsions, and depression.

Recurrent GBM

B] EF-11 Pivotal Study

Stupp et al. (2012) published data from the EF-11 trial, a prospective, multicenter, randomized, active controlled clinical trial designed to compare the safety and effectiveness outcomes of recurrent GBM patients treated with Optune to those treated with BPC chemotherapy (including bevacizumab) selected by the treating physician. A total of 237 patients were enrolled in the study from 28 clinical centers in the US and Europe. The final study analysis compared 120 Optune patients with 117 BPC chemotherapy patients.

The study objectives were:

- To prospectively compare the OS of recurrent GBM patients treated with Optune to those treated with BPC chemotherapy.
- To prospectively determine the median survival, percent one-year survival rate, PFS, PFS6, RR rate and QOL of patients treated with the Optune compared to BPC chemotherapy.
- To collect evidence of the safety of Optune for patients with recurrent GBM using Optune.

Patients with previously diagnosed GBM who had relapsed or progressed despite conventional therapy (surgery and chemo-radiotherapy followed by chemotherapy) were recruited into the study. More than 80% of patients had failed two or more prior lines of chemotherapy and 20% had failed bevacizumab prior to enrollment, a population that usually fares poorly with subsequent treatments. Patients in the treatment arm received continuous Optune treatment at home while maintaining normal daily activity. Chemotherapy treatments used in the control arm were comprised mainly of the following as single agents or in combination: bevacizumab (Avastin) or irinotecan

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(mainly in Europe) followed by nitrosureas (BCNU), platinum based chemotherapy (carboplatin), and TMZ. Patients were seen monthly and had an MRI every two months until disease progression. Mean use of Optune was 20.6 hours per day.

Study results are summarized below.

- The pivotal study data establish that Optune therapy is at least comparable to chemotherapy in extending OS for patients with recurrent GBM; 6.6 months vs. 6.0 months.
- The secondary effectiveness endpoint results support the findings of the primary endpoint; they show the Optune device is at least clinically equivalent to active chemotherapy. In summary: PFS for treatment arm was 2.2 mo. vs. 2.1 mo.; PFS6 was 21.4% vs. 15.1%; and radiological response rate (RR) rate was 14.0% vs. 9.6%.
- QOL for patients treated with Optune is significantly improved compared to patients treated with active chemotherapies. Patients in the study arm reported improved cognitive, emotional and role functioning, and a marked improvement in adverse treatment-related symptoms such as nausea and pain.
- In a clinical trial, Optune was shown to be safe and well tolerated with significantly less toxicity than existing treatment options for recurrent GBM. The most common ($\geq 10\%$) adverse events seen when using Optune alone were scalp irritation from device use and headache. The following adverse reactions were considered related to Optune when using the device alone: scalp irritation from device use, headache, malaise, muscle twitching, fall and skin ulcer.

Conclusion: The pivotal study data established that Optune produces clinically comparable outcomes to BPC chemotherapy, including bevacizumab (Roche; Avastin), across both primary OS and secondary effectiveness end-points for recurrent GBM patients. Additionally, Optune therapy results in fewer treatment related adverse events and certain QOL measures were better with Optune than compared to BSC chemotherapy.

C] Patient Registry Dataset (PRiDe)

Mrugala et al (2014) report on PRiDe a post-marketing registry of patients who received Optune Therapy for recurrent GBM in the U.S. between October 2011 and November 2013. Data were collected from all 457 recurrent GBM patients who began commercial treatment during that period. Age and gender characteristics were similar in the PRiDe and EF-11 trial. OS was collected using the Social Security Death Date Registry and obituaries. Subgroup analyses were performed on patient/clinical characteristics and found to be significantly correlated with OS. A monthly compliance assessment was

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performed for each patient using a computer download of an internal log file from the Optune device.

Study findings include the following:

- Median OS for those on Optune therapy was significantly longer in PRiDe than in the EF-11 trial (9.6 mo. vs. 6.6 mo.)
- One- and two-year OS rates for Optune therapy patients were more than double in PRiDe as compared to the EF-11 trial (1-year- 44% vs. 20%; 2-year- 30% vs. 9%).
- No new adverse events were detected in PRiDe. The most common device-related adverse event was a skin irritation beneath the transducer arrays, easily treated with topical corticosteroids.

Major median OS differences in patients registered in PRiDe compared to median OS of those treated with Optune monotherapy in the EF-11 trial led to subgroup analyses to explore reasons for the variation. These analyses suggest there may be several favorable prognostic factors that influence OS in Optune-treated patients. These include: daily compliance $\geq 75\%$, Optune therapy initiated at first recurrence, use in Bevacizumab naïve patients, and KPS ≥ 90 .

Conclusion: Understanding favorable prognostic factors may assist in appropriate patient selection for Optune

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Appendix A

FDA Approval Letters

Newly Diagnosed GBM

http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013a.pdf

Recurrent GBM

http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100034a.pdf

Appendix B

EF-14 Pivotal Trial Interim Analysis Patient Characteristics

ITT Population	Optune + TMZ (n=210)	TMZ Alone (n=105)
Characteristics		
Median age, years (range)	57 (20-83)	58 (21-80)
Female sex, n (%)	70 (33)	38 (36)
Median KPS (range)	90 (60-100)	90 (70-100)
Extent of resection, n (%)		
Gross total resection	135 (64)	67 (64)
Partial resection	52 (25)	27 (26)
Biopsy	23 (11)	11 (10)
MGMT status, n (%)		
Methylated	49 (23)	26 (25)
Unmethylated	79 (38)	38 (36)
Insufficient for testing	24 (11)	11 (10)
Not assessed	58 (28)	30 (29)
Median time from diagnosis to randomization, mo (range)	3.8 (2.0-5.7)	3.8 (1.4-5.7)
Duration of Therapy		
Median number of TMZ cycles, n (range)	6.0 (1-26)	4.0 (1-24)
Median number of Optune cycles, n (range)	9.0 (1-58)	0 (0-0)

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Appendix C Pivotal Trial Adverse Events—Interim Analysis Population

Safety Population	Optune + TMZ (n=437) n (%)	TMZ Alone (n=207) n (%)
System Organ Class		
Blood and lymphatic system disorders		
Thrombocytopenia	32 (7)	10 (5)
Leukopenia	8 (2)	1 (<1)
Lymphopenia	14 (3)	7 (3)
Neutropenia	8 (2)	3 (1)
Anemia	5 (1)	4 (2)
General disorders and administration site conditions		
Fatigue	15 (3)	7 (3)
Asthenia	7 (2)	1 (<1)
Procedural complications		
Fall	8 (2)	1 (<1)
Nervous system disorders		
Headache	10 (2)	3 (1)
Convulsion	19 (4)	11 (5)
Cognitive disorder	4 (1)	4 (2)
Hemiparesis	9 (2)	1 (<1)
Brain edema	9 (2)	6 (3)
Cerebral hemorrhage	0 (0)	4 (2)
Respiratory disorders		
Pulmonary embolism	8 (2)	7 (3)

- The most common (≥10%) adverse events involving Optune in combination with TMZ were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression

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Clinical Practice Experience With NovoTTF-100A™ System for Glioblastoma: The Patient Registry Dataset (PRiDe)

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Recurrent glioblastoma multiforme (GBM) is a highly aggressive cancer with poor prognosis, and an overall survival of 6 to 7 months with optimal therapies. The NovoTTF-100A™ System is a novel antimitotic cancer therapy recently approved for the treatment of recurrent GBM, based on phase III (EF-11) trial results. The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received NovoTTF Therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data were collected from all adult patients with recurrent GBM who began commercial NovoTTF Therapy in the United States between October 2011 and November 2013. All patients provided written consent before treatment was started. Overall survival (OS) curves were constructed for PRiDe using the Kaplan-Meier method. Median OS in PRiDe was compared for patients stratified by average daily compliance ($\geq 75\%$ v $< 75\%$ per day) and other prognostic variables. Adverse events were also evaluated. Data from 457 recurrent GBM patients who received NovoTTF Therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received NovoTTF Therapy for first recurrence (33% v 9%) and had received prior bevacizumab therapy (55.1% v 19%). Median OS was significantly longer with NovoTTF Therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 v 6.6 months). One- and 2-year OS rates were more than double for NovoTTF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% v 20%; 2-year: 30% v 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse event was detected in PRiDe. As in the EF-11 trial, the most frequent

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Conflicts of interest. Advisory Board, Novocure; research funding: Novocure (EF-14 study).

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adverse events were mild to moderate skin reactions associated with application of the NovoTTF Therapy transducer arrays. Results from PRiDe, together with those previously reported in the EF-11 trial, indicate that NovoTTF Therapy offers clinical benefit to patients with recurrent GBM. NovoTTF Therapy has high patient tolerability and favorable safety profile in the real-world, clinical practice setting.

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Glioblastoma multiforme (GBM) is the most aggressive form of human glioma and accounts for approximately 60% to 70% of all malignant gliomas.^{1,2} Based on data from the 2013 Central Brain Tumor Registry of the United States (CBTRUS) statistical report on primary brain and CNS tumors in the United States, an estimated 9,600 to 11,200 new cases of GBM will be diagnosed in 2014.^{1,2} Virtually all patients with newly diagnosed GBM relapse despite maximal multimodality treatment,³ with a median time to recurrence of approximately 7 months.⁴ The prognosis for patients with recurrent GBM is even worse. The median progression-free survival (PFS) was only 9 weeks in the pre-bevacizumab era.⁵ In 2009, bevacizumab received accelerated approval from the US Food and Drug Administration (FDA) for the treatment for recurrent GBM based on two single-arm studies with favorable response rates and PFS data.^{1,6,7} Formal phase III data is not available in the recurrent setting, however phase III comparison of bevacizumab versus placebo in newly diagnosed glioblastoma patients failed to demonstrate prolongation of survival with bevacizumab.^{1,8} A major challenge in treatment of recurrent GBM, particularly with bevacizumab, is that the tumor eventually develops resistance to the drug. Moreover, bevacizumab-treated tumors may convert to a more aggressive phenotype histologically and exhibit infiltrative tumor growth as observed on magnetic resonance imaging (MRI).^{9,10} Furthermore, patients with recurrent GBM who progress following bevacizumab therapy are typically resistant to subsequent cytotoxic chemotherapies.^{1,11,12} Therefore, new treatments that can offer a different mechanism of action and potentially overcome resistance of GBM are desperately needed.

The NovoTTF-100A™ System (Novocure, Ltd., Haifa, Israel) is a novel antimitotic cancer therapy approved in 2011 by the US FDA for the treatment of recurrent supratentorial GBM,^{13,14} based on the results of a phase III trial comparing NovoTTF Therapy with best chemotherapy according to physician choice.¹⁵ The unique mechanism of action of NovoTTF Therapy involves localized delivery of alternating low-intensity, intermediate-frequency,

tumor-treating fields (TTFields) via non-invasive transducer arrays attached to the patient's scalp.¹⁴ In preclinical studies, TTFields have been shown to selectively kill or arrest the growth of rapidly dividing cancer cells including glioblastoma cell lines by disrupting both mitotic spindle formation and normal cytokinesis by interrupting cytoplasmic furrow formation.^{16–20}

The pivotal phase III (EF-11) trial that led to FDA approval of the device compared NovoTTF Therapy (n = 120) with best chemotherapy according to physician's choice (n = 117) in recurrent GBM patients from 28 institutions in seven countries.¹⁵ More than 80% of patients in the study had failed two or more prior chemotherapies, and 20% had experienced recurrence while on bevacizumab. Seventy-eight percent of the 116 patients who started NovoTTF Therapy completed at least one full-treatment course (4 weeks). The results demonstrated comparable median OS with NovoTTF Therapy compared with chemotherapy (6.6 v 6.0 months; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.66 to 1.12; *P* = .27), together with fewer severe adverse events (6% v 16%, *P* = .022) and improved quality-of-life measures for the NovoTTF Therapy arm compared with chemotherapy. The most common adverse events with NovoTTF Therapy were mild to moderate skin irritation associated with the transducer arrays. Systemic adverse events commonly associated with chemotherapy were generally absent in patients receiving NovoTTF Therapy.

Given the mechanism of action of TTFields and the results of preclinical studies, optimal device compliance is required for therapeutic effectiveness with NovoTTF Therapy. NovoTTF Therapy does not have a half-life, therefore it requires continuous application to exert a therapeutic effect. This differs from systemic chemotherapy, which exerts anticancer effects between administrations due to the drug pharmacokinetics. Based on modeling of tumor growth kinetics and supporting preclinical and clinical data, NovoTTF Therapy must be administered almost "continuously" for at least 4 weeks in order to halt tumor growth and subsequently demonstrate an objective response.^{21,22} Recommended administration of NovoTTF Therapy

is ≥ 18 hours per day for each 4-week treatment cycle.²¹ A post hoc analysis of the phase III trial data recently showed significantly longer median OS in NovoTTF Therapy patients with a maximal monthly compliance rate $\geq 75\%$ (≥ 18 hours daily) versus those with a $< 75\%$ compliance rate (7.7 *v* 4.5 months, $P = .042$) (see Kanner in this supplement). A recent responder analysis also demonstrated very high compliance rates $> 90\%$ in EF-11 responders.²³

The Patient Registry DataSet (PRiDe) is a registry of 457 recurrent GBM patients who received NovoTTF Therapy in the clinical practice setting on the US commercial prescription-use program between October 2011 and November 2013. Patients treated in clinical trials often differ from those who receive treatment in the real-world setting due to patient selection criteria and frequently represent a less homogenous group. Hence registry data can be an important source of additional information about the efficacy and safety of a newly approved therapy. This report analyzes data from PRiDe to help us better understand the potential benefits of NovoTTF Therapy for patients with recurrent GBM, including analyses of median OS, tolerability, and the relationship between survival and compliance as well as other prognostic factors.

METHODS

Patients and Data Collection

PRiDe data were collected from all patients ≥ 18 years old with recurrent GBM who began commercial treatment with NovoTTF Therapy in the United States between October 2011 and November 2013. All participating patients provided written informed consent to use protected health information to advance the understanding of NovoTTF Therapy. Recurrent GBM was defined as histologically-confirmed, supratentorial GBM (World Health Organization grade IV astrocytoma) with radiologically confirmed evidence of disease progression, as defined by the Macdonald criteria,²⁴ following treatment with radiotherapy with or without concomitant and/or adjuvant chemotherapy. Patients who received NovoTTF Therapy were not restricted to the number or types of prior therapies or recurrences. Information about combination use of NovoTTF Therapy as part of the prescription-use program was not captured. Therefore some patients may have received combination therapy (chemotherapy or anti-vascular endothelial growth factor [VEGF] agents) rather than monotherapy.

Baseline characteristics were assessed by manual patient chart review. OS was collected using the Social Security Death Date Registry and obituaries. Novocure started collecting compliance data centrally

in January 2013, so such data are only available for under two thirds of patients in the registry. A monthly compliance assessment was performed for each patient by computer download of an internal log file which captures the cumulative amount of time therapy is delivered to the patient. Patient compliance was calculated as the average percentage of each day the system was delivering fields (out of each 24-hour period). In addition, other prognostic factors, such as the number of prior recurrences, age, KPS, prior bevacizumab use, and any debulking surgery were captured and analyzed. Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria. Quality-of-life measures were not assessed in PRiDe.

Statistical Analysis

The OS and treatment duration curves were constructed using the Kaplan-Meier method. OS in PRiDe was compared to OS for patients receiving NovoTTF Therapy or best chemotherapy in the phase III EF-11 trial (ITT population) using a log-rank (Mantel-Cox) test. Patient or disease characteristics prognostic for survival with NovoTTF Therapy were assessed using a Cox proportional hazards model (P value of .15 for significant interactions). Subgroup analyses were performed on patient/clinical characteristics found to be significantly correlated with OS. A log-rank test was used to compare the relationship between OS and daily compliance ($< 75\%$ *v* $\geq 75\%$), prior debulking surgery (yes, no), KPS (90–100, 70–80, 10–60), recurrence number (1st, 2nd, 3rd–5th recurrence) and prior bevacizumab use (prior use *v* naïve).

RESULTS

Patient Characteristics

Four-hundred fifty-seven patients with recurrent GBM were treated with NovoTTF Therapy between October 2011 and November 2013 at 91 oncology centers. This population is more than three times the 120 subjects treated with NovoTTF monotherapy, as well as the 117 subjects treated with chemotherapy, in the phase III EF-11 trial, from which we were making a comparison. Baseline patient characteristics are presented in Table 1. Patient characteristics (age and gender) were generally similar in PRiDe and the two treatment groups in the EF-11 trial. Approximately one third of patients treated commercially with NovoTTF Therapy were women, which is an important observation given the perceived cosmetic considerations of head shaving and array placement.

Table 1. Baseline Patients and Clinical Characteristics for Patients With Recurrent Glioblastoma Multiforme in PRiDe and EF-11 Trial

Characteristic		PRiDe NovoTTF Therapy (n = 457)	EF-11 NovoTTF Therapy (n = 120)	EF-11 Chemotherapy (n = 117)
Age (y)	Median (range)	55 (18–86)	54 (24–80)	54 (29–74)
Gender	Male	67.6%	77%	62%
	Female	32.4%	23%	38%
KPS	Median (range)	80 (10–100)	80 (50–100)	80 (50–100)
	10–60	19.0%	NA	NA
	70–80	46.6%	NA	NA
	90–100	30.9%	NA	NA
	Unknown	3.5%	NA	NA
Recurrence	Median (range)	2 (1–5)	2 (1–5)	2 (1–4)
	First	33.3%	9%	15%
	Second	26.9%	48%	46%
	Third to Fifth	27.4%	43%	39%
Prior treatments	Unknown	12.5%	0%	0%
	Bevacizumab	55.1%	19%	18%
	RT + temozolomide	77.9%	86%	82%
	Debulking surgery	63.9%	79%	85%
	Carmustine wafers	3.7%	NA	NA

Abbreviations. KPS, Karnofsky performance status; NA, not applicable; RT, radiotherapy.

Tolerability and Safety

No new adverse events were detected in PRiDe compared to those found in EF-11. The most common device-related adverse events associated with NovoTTF Therapy in the registry were skin reactions/irritation and heat sensations on the scalp beneath the transducer arrays (Table 2). Patients sometimes described these events as "warmth" or "tingling" sensations, none of which were associated with injury to the patient. Systemic adverse events, which were often associated with chemotherapy (eg, gastrointestinal, hematologic, and infectious adverse events), were rare for patients treated with NovoTTF Therapy in the registry.

Survival Rates

Figure 1 presents Kaplan-Meier curves of OS for patients treated with NovoTTF Therapy in the clinical practice setting (PRiDe) and those who received NovoTTF Therapy or best chemotherapy as part of the EF-11 trial (ITT population). Median OS on NovoTTF Therapy appeared to be markedly longer in PRiDe than in the EF-11 trial (9.6 v 6.6 months). Median OS was also significantly longer with NovoTTF Therapy in PRiDe than with best chemotherapy group in the EF-11 trial (9.6 v 6.0 months). One- and 2-year OS rates for NovoTTF Therapy patients in PRiDe were more than double

those seen with either NovoTTF Therapy or best chemotherapy in the EF-11 trial (Table 3).

Median treatment duration for patients in PRiDe was 4.1 months (95% CI, 3.5–4.8). In comparison, the median treatment duration in the EF-11 study was 2.3 months (95% CI, 2.1–2.4) for NovoTTF Therapy arm and 2.1 months (95% CI, 2.0–2.9) for best chemotherapy. Figure 2 shows the fraction of NovoTTF Therapy patients still on treatment over time. Roughly 50% were still on NovoTTF Therapy after 4 months from treatment start, and roughly 10% were still on NovoTTF Therapy at 2 years after treatment start.

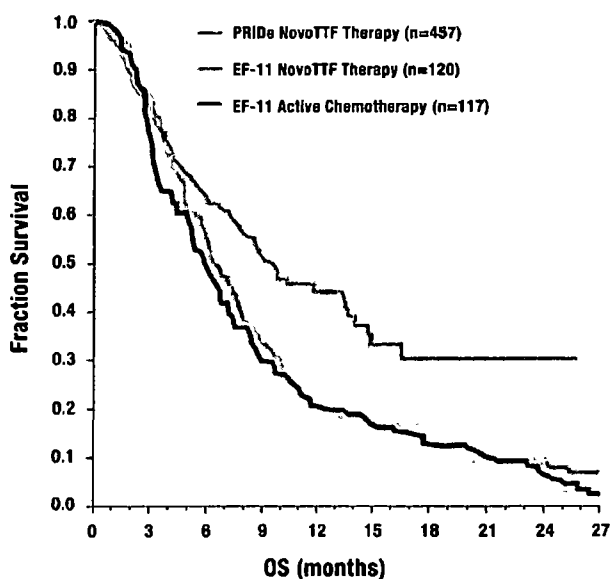
Compliance as a Prognostic Factor and Its Relationship to OS

Because of the major difference in the OS in patients registered in PRiDe as compared to the OS of subjects treated with NovoTTF monotherapy in EF-11, we sought to identify the prognostic factors in the former cohort. The first prognostic factor we analyzed was NovoTTF treatment compliance because it was found to be prognostically important in EF-11 in post hoc analysis. Compliance data was collected centrally starting in January 2013 and, therefore, were only available for 287 of the 457 patients (63%) in the registry. The median daily compliance was 70% for patients treated with NovoTTF Therapy in PRiDe (range, 12%–99%). One

Table 2. Adverse Events in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe

Adverse event	Percentage of Patients PRiDe (n = 457)
Skin reaction	24.3
Heat sensation	11.3
Neurological disorder	10.4
Seizure	8.9
Electric sensation	7.7
Headache	5.7
Pain/discomfort	4.7
Fall	3.9
Psychiatric disorder	2.9
Gastrointestinal disorder	2.9
Fatigue	2.5
Vascular disorder	1.6
Weakness	1.4
Infections	1.4
Eye disorder	1.3

hundred twenty-seven (44%) with available data achieved daily compliance of $\geq 75\%$ of each day, while 160 (56%) had daily compliance of $< 75\%$. As illustrated in Figure 3, median OS was significantly longer in patients with a NovoTTF Therapy daily compliance $\geq 75\%$ than in those with $< 75\%$ daily compliance (13.5% ν 4.0%; HR, 0.43; 95% CI, 0.29–0.63; $P < .0001$).

**Figure 1.** Kaplan-Meier overall survival (OS) curves for patients with recurrent glioblastoma multiforme treated with NovoTTF Therapy in PRiDe or with NovoTTF Therapy or best chemotherapy in the EF-11 trial.**Other Prognostic Factors**

The Cox proportional hazards model identified the presence or absence of debulking surgery, number of prior recurrences, compliance, KPS, and prior bevacizumab therapy as significant independent predictors of OS in patients treated with NovoTTF Therapy in PRiDe ($P < .15$). Table 4 presents log-rank OS testing between patient subgroups in PRiDe for each of these prognostic factors; Figure 4 presents Kaplan-Meier survival curves for these same factors. First, no difference in median OS was observed between patients who did not have surgical debulking and those who did (8.9 ν 9.8, respectively; HR, 1.1; 95% CI, 0.8–1.5; $P = .7927$). Second, recurrent GBM patients treated with NovoTTF Therapy in clinical practice at their first recurrence experienced a significantly longer median OS as compared to patients treated at their second, third, or subsequent recurrence (20 months compared to 8.5 and 4.9 months, respectively; HR, 0.6; 95% CI, 0.4–0.9; $p = 0.0271$ and HR, 0.3; 95% CI, 0.2–0.5; $P < .0001$). It should be noted that a greater percentage of patients in PRiDe were at their first GBM recurrence compared with patients treated with NovoTTF Therapy or best chemotherapy in the EF-11 trial (33.3% ν 9% and 15%, respectively). In addition, differences were also apparent between patients in PRiDe and those in the EF-11 trial with respect to prior treatments. More than half of NovoTTF Therapy patients in PRiDe had previously received bevacizumab (55.1%), compared with only 19% of NovoTTF monotherapy and 18% of best active chemotherapy cohorts in the EF-11 trial. Third, recurrent GBM patients with KPS ≥ 90 experienced a near doubling of median OS compared with patients with a KPS of 70–80, median OS 14.8 versus 7.7 months, respectively, HR 0.6 (95% CI, 0.4–0.9), $P = .0070$. Lastly, the survival of bevacizumab-naïve patients was significantly longer compared to patients who had received prior bevacizumab before starting NovoTTF Therapy, with a respective median OS 13.4 versus 7.2 months, HR 0.5 (95% CI, 0.4–0.7), $P < .0001$. These data suggest

Table 3. One- and 2-Year Survival Rates for Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe and EF-11 trial, and With Best Chemotherapy in the EF-11 Trial

Endpoint	PRiDe NovoTTF Therapy (n = 457)	EF-11 NovoTTF Therapy (n = 120)	EF-11 Chemo- therapy (n = 117)
1-Year survival	44%	20%	20%
2-Year survival	30%	9%	7%

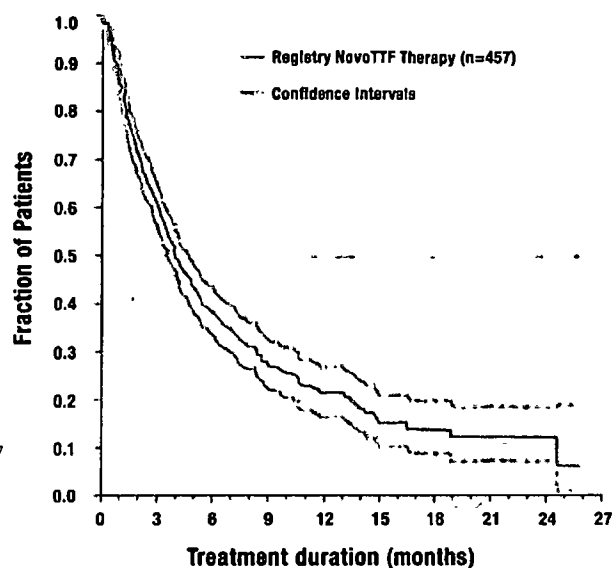


Figure 2. Fraction of NovoTTF Therapy patients alive by treatment duration (PRiDe).

that, within this heterogeneous group of patients registered in PRiDe, there were many patients who derived significant benefit from NovoTTF Therapy.

DISCUSSION

The Patient Registry Dataset, or PRiDe, represents 457 unselected patients with recurrent GBM who received NovoTTF Therapy in a real-world, clinical practice setting across 91 cancer centers in the United States between October 2011 and November 2013. No new, unexpected adverse event was detected with NovoTTF Therapy in this cohort. Similar to those found in the EF-11 trial,¹⁵ the most common adverse events associated with NovoTTF Therapy were mild to moderate skin reactions localized to the scalp beneath the transducer arrays. These reactions were easily treated with topical corticosteroids or antibiotics, were not associated with serious injury to the scalp, and typically did not require interruption of treatment. Some patients in PRiDe reported subjective sensations beneath the transducer arrays, often described as "warmth" or "tingling." These heat or electric sensations were captured as adverse events in PRiDe ("skin reaction"), but not in the EF-11 trial. These sensations occur when the contact between transducer arrays and the skin is suboptimal, and usually indicate the presence of hair regrowth. In these instances, re-shaving the head can re-establish optimal contact between the skin and transducer arrays. Furthermore, systemic adverse events commonly observed with chemotherapy were largely absent in patients

treated with NovoTTF Therapy in PRiDe as they were in the EF-11 trial.¹⁵

Patients receiving NovoTTF Therapy for recurrent GBM demonstrated a median OS of 9.6 months in clinical practice. This compares favorably to the reported median OS for the EF-11 pivotal trial cohort treated with NovoTTF monotherapy, where median OS was 6.6 months, and to OS of patients who received treatments for recurrent GBM in other clinical trials.²⁵⁻²⁸ For example, recent reports of median OS in recurrent GBM patients treated with bevacizumab are in the range of 6 to 10.5 months,^{7,12,25-27,29} and those treated with temozolomide in the range 6 to 9 months.³⁰⁻³² It should be noted that many of the longer term survivals noted in clinical trials of bevacizumab and temozolomide in recurrent GBM included small sample sizes and none were randomized.

The difference between the OS seen in clinical practice and in the EF-11 trial may in part be due the greater percentage of patients with a first GBM recurrence in PRiDe versus patients in the EF-11 study (33.3% v 9%, respectively). This observation is also supported by a prior post hoc analysis of EF-11 that showed a significantly longer median OS in patients treated with NovoTTF Therapy at their first or second recurrence compared to those treated at third or subsequent recurrences. Furthermore, when used as intended (daily compliance $\geq 75\%$ or ≥ 18 hours daily), the median OS for patients treated with NovoTTF Therapy in PRiDe was remarkably high at 13.5 months compared to only 4.0 months in those who had suboptimal compliance (daily compliance $< 75\%$ or < 18 hours daily). Kanner et al (see accompanying Kanner article in this supplement)

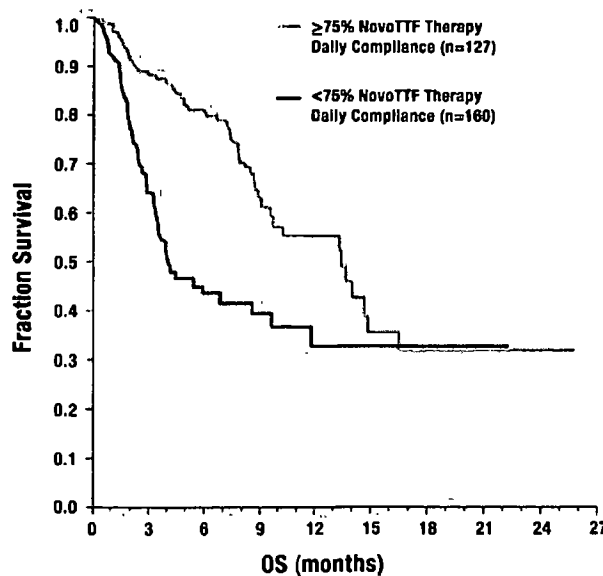


Figure 3.

Table 4. Results of Subgroup Analyses of Overall Survival (OS) in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe Based on Prognostic Factors Significantly Correlated With OS in the Cox Proportional Hazards

Variable	Median OS (mo)	Hazard Ratio	P Value
No. of recurrences			
1st	20	—	—
2nd	8.5	0.6 (95% CI, 0.4–0.9)	.0271 ^a
3rd–5th	4.9	0.3 (95% CI, 0.2–0.5)	<.0001 ^b
Compliance			
≥ 75%	13.5	0.4 (95% CI, 0.3–0.6)	<.0001
< 75%	4.0		
Karnofsky performance status (KPS)			
90–100	14.8	—	—
70–90	7.7	0.6 (95% CI, 0.4–0.9)	.0070 ^c
10–60	6.1	0.4 (95% CI, 0.2–0.6)	<.0001 ^d
Bevacizumab use			
Naïve	13.4	0.5 (95% CI, 0.4–0.7)	<.0001
Prior use	7.2		
Debulking surgery			
No	8.9	1.1 (95% CI, 0.8–1.5)	.7927
Yes (any surgery)	9.8		

^a First recurrence compared to 2nd recurrence.^b First recurrence compared to 3rd–5th recurrence.^c KPS 90–100 compared to KPS 70–80.^d KPS 90–100 compared to KPS 10–60.

recently reported similar findings when re-examining data from the EF-11 trial: median OS was significantly longer with a monthly compliance rate for NovoTTF Therapy ≥ 75% than < 75% (7.7 v 4.5 months, $P = .042$). The compliance findings from each of these studies are consistent with the mechanism of action of NovoTTF Therapy, which depends on almost continuous administration (≥ 18 hours per day) for a prolonged period of time (≥ 4 weeks).^{21,22} However, patients in PRiDe who had suboptimal compliance were also found to have lower KPS and were, in general, at later stages of their disease. It is unclear whether they also may have had larger tumors or inadequate social support. Nevertheless, consistent with previous findings, our data suggest that applying NovoTTF Therapy to patients with higher performance status, earlier in their recurrence and ensuring treatment compliance, can maximize clinical benefit.

Additional analyses uncovered other prognostic factors that were important for patients in PRiDe. Of interest, in our subgroup analysis, 55.1% of patients in PRiDe who received prior bevacizumab therapy demonstrated a shorter median OS of 7.2 months, as compared to a median OS of 13.4 months in bevacizumab-naïve patients. The shorter survival in patients treated previously with bevacizumab may be a result of acquired tumor resistance and development of a more aggressive phenotype with infiltrative tumor progression on MRI.^{9,10} Moreover,

patients with recurrent GBM tumors that progress while on bevacizumab therapy are typically resistant or refractory to subsequent cytotoxic chemotherapy,^{1,11,12} and have a median OS of just 2.7 months. Therefore, the PRiDe data suggest that at least a percentage of bevacizumab-resistant tumors remain responsive to NovoTTF Therapy. Future analysis of responders and nonresponders to NovoTTF Therapy will need to include molecular genetic analysis of the tumor (and especially MGMT methylation status), the estimated tumor size (volume) as measured by fluid attenuated inversion recovery sequence on MRI, and more detailed analysis of the extent of resection.

Our analysis of KPS in PRiDe also demonstrated that higher KPS correlated with longer OS. It is unclear at this time whether or not patients who had KPS 90–100 had smaller tumors than the rest of the cohort or perhaps more extensive resections. KPS is often, but not always, a measure of tumor size, particularly the microscopic invasive component of the glioblastoma. Whether or not the median tumor size, as measured by gadolinium-enhanced T1-weighted and/or FLAIR MRI, differ between the subgroup with KPS 90–100 versus 70–90 and 10–60 remains to be determined. Of note, age was not a predictor of OS in the PRiDe dataset when evaluated either by direct correlation (Pearson correlation coefficient) or a Cox proportional hazards model ($P = .20$). In addition, age was

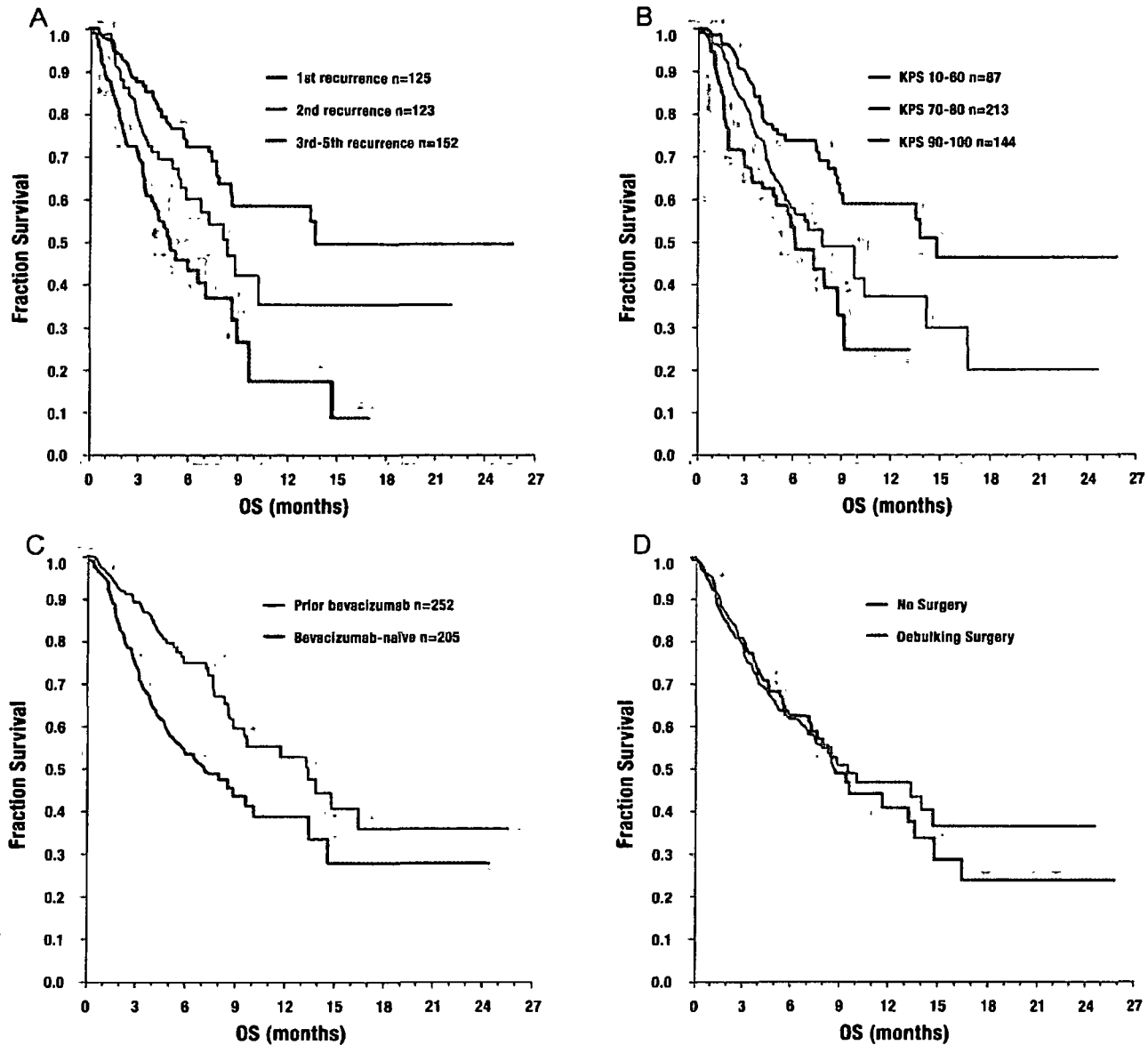


Figure 4. Kaplan-Meier overall survival (OS) curves for recurrent glioblastoma multiforme patients treated with NovoTTF Therapy in PRiDe based on (A) recurrence number, (B) Karnofsky performance status (KPS), (C) prior bevacizumab use, and (D) prior debulking surgery, respectively.

not correlated with compliance in the PRiDe (correlation coefficient = 0.02; $P = .37$). Taken in the context of the overall efficacy results, these findings suggest NovoTTF Therapy works well for patients of all ages and that advanced age is not associated with lower compliance. It would also be interesting to know if marital status (or other measures of patient support) influence compliance and survival, but data on marital status were not collected in PRiDe.

Finally, the PRiDe dataset did not capture patients on combination treatments in which additional biologic therapy or chemotherapy were added to

NovoTTF Therapy in a combined regimen. It is possible that the longer survival seen in clinical practice with NovoTTF Therapy compared to NovoTTF monotherapy in the EF-11 trial is a reflection of combination use of NovoTTF Therapy with biological agents or cytotoxic chemotherapy. In fact, preclinical data have suggested that TTFIELDS are additive or even synergistic with chemotherapies in cell culture.³³⁻³⁵ Therefore, the potential benefits of combining NovoTTF Therapy with other systemic therapies warrant further investigation. A phase III trial of NovoTTF Therapy together with temozolomide compared to temozolomide alone is currently

ongoing in patients with newly diagnosed glioblastoma. The results of this trial will shed light on the possible additive effects of NovoTTF Therapy and systemic chemotherapy.

In summary, PRiDe and the EF-11 trial represent one of the largest datasets of patients with recurrent GBM published to date, containing 700 patients in total, 567 of whom were treated with NovoTTF Therapy. The results, individually and collectively, provide further support for the use of NovoTTF Therapy to treat recurrent, supratentorial GBM. Observations from the post-marketing registry demonstrate that the safety and efficacy observed with NovoTTF Therapy in a clinical trial extend to the real-world, clinical practice setting. Future investigations may need to include NovoTTF Therapy in combination with other recurrent GBM treatments, which together may have additive or synergistic effects on patient outcome.

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An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas

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Opinion statement

Glioblastoma is a deadly disease and even aggressive neurosurgical resection followed by radiation and chemotherapy only extends patient survival to a median of 1.5 years. The challenge in treating this type of tumor stems from the rapid proliferation of the malignant glioma cells, the diffuse infiltrative nature of the disease, multiple activated signal transduction pathways within the tumor, development of resistant clones during treatment, the blood brain barrier that limits the delivery of drugs into the central nervous system, and the sensitivity of the brain to treatment effect. Therefore, new therapies that possess a unique mechanism of action are needed to treat this tumor. Recently, alternating electric fields, also known as tumor treating fields (TTFields), have been developed for the treatment of glioblastoma. TTFields use electromagnetic energy at an intermediate frequency of 200 kHz as a locoregional intervention and act to disrupt tumor cells as they undergo mitosis. In a phase III clinical trial for recurrent glioblastoma, TTFields were shown to have equivalent efficacy when compared to conventional chemotherapies, while lacking the typical side effects associated with chemotherapies. Furthermore, an interim analysis of a recent clinical trial in the upfront setting demonstrated superiority to standard of care cytotoxic chemotherapy, most likely because the subjects' tumors were at an earlier stage of clonal evolution, possessed less tumor-induced immunosuppression, or both. Therefore, it is likely that the efficacy of TTFields can be increased by combining it with other anti-cancer treatment modalities.

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Introduction

Tumor treating fields (TTFields) represent a novel treatment modality for cancer that utilizes alternating electric fields at an intermediate frequency of 200 kHz. At this specific frequency, TTFields have been shown to penetrate into the head from the surface of the scalp. Computational modeling also showed that the fields are distributed inhomogeneously within the supratentorial regions of the brain, and they tend to become intensified near the ventricles [1•]. At the cellular level, the electromagnetic energy perturbs proteins that have large dipole moments. Cells treated with TTFields exhibited a variety of abnormalities indicative of mitotic catastrophe and aberrant mitotic exit, including cells in polyploidy prophase, rosettes, multi-spindled metaphase, single-spindled metaphase, and asymmetric anaphase [2]. Indeed, cells exhibit violent membrane blebbing as they enter anaphase and attempt to divide. This results in aberrant mitotic exit and subsequent cell death [3••]. Some of the proteins that are critical for the proper progression through mitosis have sufficiently high dipole moments to suggest that they may be targets of TTFields, including the mitotic septin complex and the α/β -tubulin monomeric subunit of tubulin. Septins constitute a family of GTP-binding proteins and septin 2, 6, and 7 oligomerize into a heterotrimer with an extremely large dipole moment of 2711 Debyes [4]. Importantly, this septin complex is required for functions that are necessary for the later stages of cell division. Septin 2, 6, and 7 heterotrimers rapidly polymerize and structurally organize within the cytokinetic furrow as cells exit metaphase.

Once it is recruited, it then organizes contractile elements within the cytokinetic furrow above the equatorial cleavage plane by binding to F-actin filaments and spatially regulates myosin activation. RNAi-directed depletion of septin subunits of the heterotrimer results in mitotic catastrophe similar to that seen when cells attempt to divide in the presence of TTFields [5]. We have shown that TTFields disrupt the ability of septins to re-localize to the cytokinetic furrow and reduce the accumulation of F-actin [3••]. Therefore, TTFields affect tumor cells by interfering with their ability to complete mitosis by exerting electromagnetic induction forces that interfere with the function of proteins with high dipole moments [2, 3••].

TTFields therapy has been shown to have equivalent efficacy when compared to the best physician's choice chemotherapy in a registration phase III clinical trial for recurrent glioblastoma [6]. This led to the FDA approval on April 8, 2011 for recurrent glioblastoma [http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034a.pdf]. Interim analysis of the most recent phase III study in the newly diagnosed setting showed a significant improvement of outcomes leading to a crossover of subjects from the control arm to the experimental arm of the trial [7]. Here, we review our current understanding of the mechanisms of TTFields therapy, particularly from the physics and cell biology perspectives, as well as the available clinical data when it is applied to the treatment of glioblastoma.

Electric field distribution within the brain

At a frequency of 200 kHz, the electric fields from the surface of the scalp can permeate into the brain. This is because the penetration of electromagnetic waves through any medium is frequency dependent. Past analyses have shown that the permittivity values were similar among the calvarial bone, gray matter, and white matter, while the conductivity values varied somewhat among these three structures [8].

The electric field intensity was directly measured in a patient receiving TTFields therapy while undergoing surgery for obstructive hydrocephalus from a large pineal meningioma at the Rambam Medical Center in Haifa, Israel. The measured intensity of electric field was validated to within 10 % of the simulated value using finite element method simulation [9].

Using finite element analysis, 3-dimensional mapping of the electric field distribution within the brain revealed inhomogeneous distribution of the fields, with a higher field strength near the ventricular horns that is most likely a result of the high conductivity of the cerebrospinal fluid (Fig. 1).

Cell biology effects of alternating electric fields on dividing tumor cells

TTFields disrupt the mitotic process in dividing tumor cells that results in violent membrane blebbing [3••, 10]. This results in the disordering of chromosomes from the metaphase plate during late metaphase or early anaphase, followed by aberrant mitotic exit in the absence of cytokinesis resulting in multinucleated cells and subsequent apoptosis [3••].

The septin 2, 6, and 7 family members heterotrimerize into a protein complex that possesses an extremely large dipole moment of 2711 Debyes, and it is active in mitosis [4]. This complex serves to regulate contractile function within the cytokinetic furrow, and it is likely to provide tensile strength needed within the submembranous cortical cytoskeleton to restrain the hydrostatic pressures within the cytoplasm during cell division. It has been shown to be a target of alternating electric fields, and the disruption of this protein results in disordered segregation of chromosome and cytoplasmic contents [3••].

Following TTFields-induced aberrant mitotic exit, cells exhibit signs of cellular stress that mark them for immune destruction and facilitate immune activation. Specifically, this type of cellular stress causes increased cell surface expression of the endoplasmic reticulum chaperonin calreticulin and the secretion of HMGB1 that acts as a danger signal when released from cells [11]. The presence of calreticulin on the plasma membrane is also seen in virally infected cells, as well as tumor cells exposed to certain chemotherapy agents [12]. This has been termed "immunogenic cell death" to differentiate it from apoptosis, which is immunosuppressive. Immunogenic cell death leads to tumor destruction.

There is a compelling evidence that TTFields increase the anti-tumor immunogenicity in vivo. When highly metastatic VX-2 tumors were injected into the kidney capsule of rabbits and treated with TTFields for 7 days then allowed to grow for an additional 21 days, the number of pulmonary metastases was significantly reduced when compared to untreated control animals [13]. When the lung metastases were recovered from animals, there was increased infiltration of immune cells in the TTFields-treated metastases as compared with the non-treated ones [14].

Treatment

The management of malignant gliomas should be undertaken in a multimodal fashion, with neurosurgical input, radiation oncology expertise, and chemotherapy administration. Now, with the availability of alternating electric fields therapy as a fourth modality of treatment, neuro-oncologists will need to factor in this therapy within the spectrum of available treatments. For newly diagnosed malignant gliomas, maximal safe neurosurgical resection is still

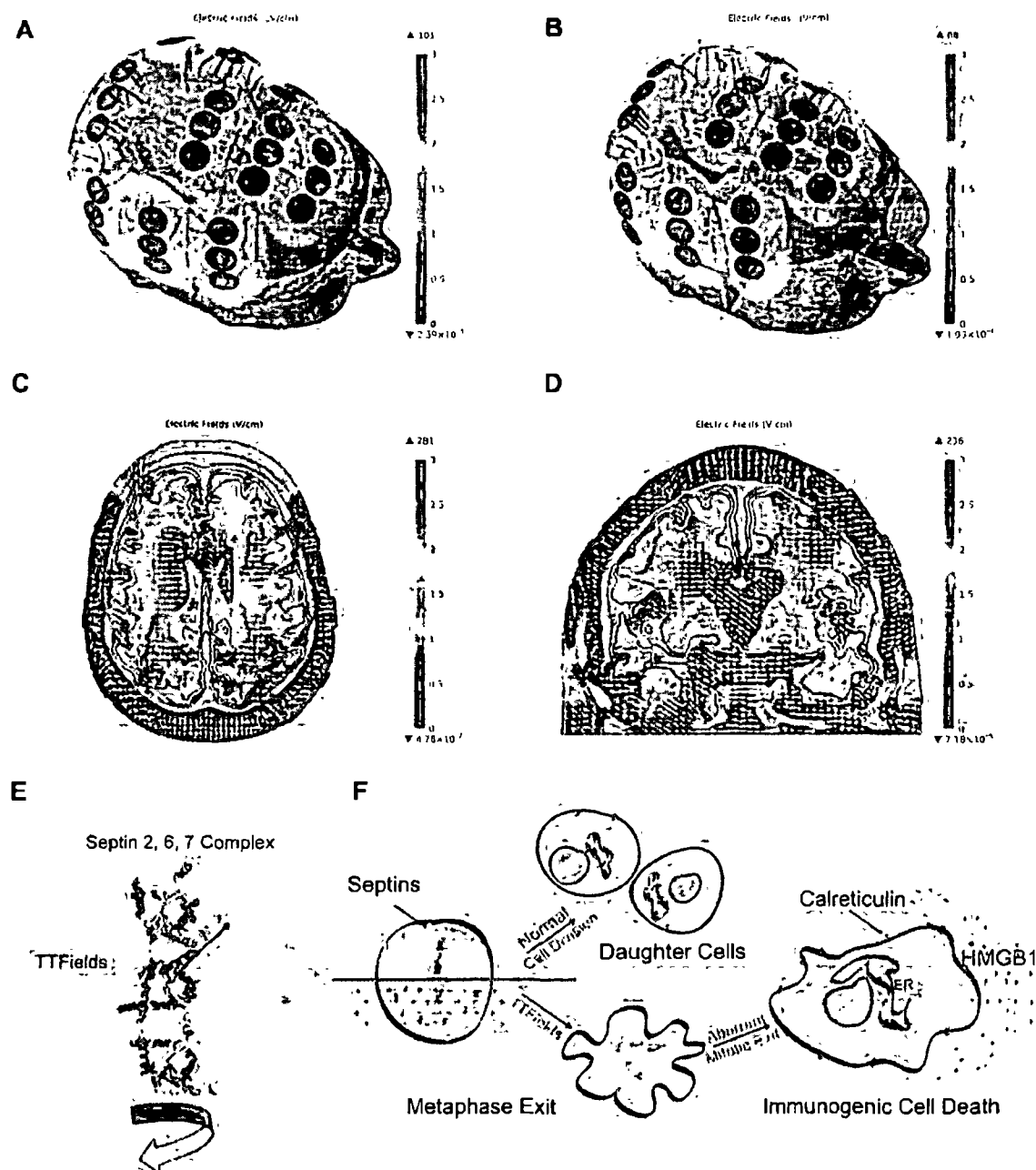


Fig. 1. A 3-dimensional render of a human head with TTFields clinically applied via electrode arrays on a glioblastoma patient whose gross tumor volume is on the right side. **a** Streamlines showing the magnitude of the electric field and direction of the current emanating from each electrode on the surface of the scalp. **b** Red arrows indicating vector field of the electric field distribution inside the brain. The intracranial electric fields are displayed in **c** axial and **d** coronal planes. **e** TTFields induce a force on the septin 2, 6, and 7 complex that has an extremely large dipole moment of 2711 Debyes. **f** This results in mitotic catastrophe and aberrant mitotic exit, leading to an increased cell surface expression of the endoplasmic reticulum chaperonin calreticulin and the secretion of HMGB1 that acts as a danger signal when release from cells, both of which are essential for immunogenic cell death.

recommended and resection accomplishes two goals of establishing a histological diagnosis and achieving cytoreduction. Although it has not been subjected to a randomized clinical trial, the best evidence for a benefit of cytoreduction is based on a retrospective analysis showing a 4.2-month survival advantage in patients with at least a 98 % resection versus those with less than 98 % [15]. However, if safe resection is not possible, biopsy to obtain a histological diagnosis is still indicated. Once a diagnosis of glioblastoma is established, patients proceed to standard of care treatment, which consists of external beam, involved-field cranial radiotherapy plus concomitant daily temozolomide, followed by 6 cycles of adjuvant temozolomide [16]. Alternatively, patients may be enrolled in a clinical trial at initial diagnosis and, depending on the conduct of the trial, may either receive treatment independently or in conjunction with standard of care treatment. Although upfront treatment can provide a period of stabilization for the glioblastoma, recurrence is the rule and additional treatments are typically needed to control tumor progression, alleviate neurological deficits, or both.

At the time of tumor recurrence, patients with a Karnofsky performance score of 70 or higher may be eligible for clinical trials. Those who are ineligible can be treated with single-agent bevacizumab or TTFields therapy since both were approved by the FDA for recurrent glioblastoma in 2009 and 2011, respectively. The benefit of bevacizumab was based on two single-arm phase II studies demonstrating a radiographic response rate of 30–40 % [17, 18]. However, infiltrative glioblastoma is the typical pattern of relapse and salvage chemotherapy after bevacizumab failure only offered a median overall survival of 5.2 months and progression-free survival of 2.0 months [19]. Therefore, alternative treatments are desperately needed for this population and TTFields therapy was demonstrated to have equivalent efficacy when compared to chemotherapy in this setting [6]. However, the optimal use of this device and its combination with conventional treatments are awaiting further investigation. Here, we review the currently available clinical data when it is applied to the treatment of glioblastoma, which is also summarized in Table 1.

TTFields therapy for recurrent glioblastoma

At present, the only indication approved by the FDA is for the treatment of recurrent glioblastoma. This is based on the registration phase III clinical trial (ClinicalTrials.gov: NCT00379470) demonstrating equivalent efficacy between TTFields therapy and best physician's choice chemotherapy (based on the best available treatment as offered by the treating physician) [6].

The primary endpoint of the trial was overall survival, and the median overall survival was 6.6 months for TTFields ($n=120$) versus 6.0 months for the best physician's choice chemotherapy ($n=117$), with a hazard ratio of 0.86 (95 % CI 0.66–1.12; $P=0.27$). It is notable that 31 % of the BPC cohort received bevacizumab alone or in combination with chemotherapy. The median progression-free survival of TTFields and the best physician's choice chemotherapy was 2.2 and 2.1 months, respectively, with a hazard ratio of 0.81 (95 % CI 0.60–1.09; $P=0.16$), and the progression-free survival at 6 months was 21.4 % (95 % CI 13.5–29.3) and 15.1 % (95 % CI 7.8–22.3), respectively ($P=0.13$). One year survival rate was 20 % in both cohorts.

Table 1. Summary of clinical data on TTFields treatment for malignant gliomas

Phase III trial for newly diagnosed glioblastoma interim analysis	TTFields treatment + temozolomide	Temozolomide alone	Hazard ratio	P
Overall survival, median ^a	19.6 months	16.6 months	0.75	0.03
Progression-free survival ^a	7.1 months	4.0 months	0.63	<0.01
Phase III recurrent glioblastoma	TTFields treatment (n=120)	Active chemotherapy (n=117)		
Overall survival, median ^b	6.6 months	6.0 months	0.86 (95 % CI 0.66–1.12)	0.27
1-year survival	20 %	20 %		
2-year survival	8 %	4 %		
3-year survival	5 %	1 %		
Prognostic factors, median overall survival ^c				
Prior bevacizumab failure	6.0 months (n=23)	3.3 months (n=21)	0.43 (95 % CI 0.22–0.85)	0.02
Prior low-grade glioma	25.3 months (n=12)	7.7 months (n=9)	0.31 (95 % CI 0.09–0.99)	0.05
Tumor size ≥18 cm ²	5.6 months (n=39)	3.3 months (n=41)	0.53 (95 % CI 0.32–0.85)	<0.01
Karnofsky performance status ≥80	7.9 months (n=83)	6.1 months (n=77)	0.71 (95 % CI 0.51–0.99)	0.05
TTFields treatment versus bevacizumab	6.6 months (n=120)	4.9 months (n=36)	0.64 (95 % CI 0.41–0.99)	0.05
Progression-free survival, median ^b	2.2 months	2.1 months	0.81 (95 % CI 0.60–1.09)	0.13
PFS at 6 months	21 %	15 %		
Responders ^d	14	7		
Response status, median overall survival				
Partial and complete response versus	24.7 months (n=14)		0.28 (95 % CI 0.14–0.58)	<0.01
Stable disease	7.6 months (n=34)		0.24 (95 % CI 0.14–0.42)	<0.01
Progressive disease	5.5 months (n=59)			
Prognostic factor in TTFields treatment responders ^e				
Overall survival, median				
With prior low-grade glioma	27.7 months			
Without prior low-grade glioma	16.6 months			
Daily dexamethasone dose, median				
Responders	1.0 mg			
Nonresponders	5.2 mg			
Cumulative dexamethasone dose, median				
Responders	7.1 mg			
Nonresponders	261.7 mg			
Treatment-related adverse events, ≥grade 2 ^{b,f}				
Hematological	3 %	17 %		
Gastrointestinal	4 %	17 %		
Dermatological	2 %	0 %		
Nervous system disorders	30 %	28 %		
Recurrent glioblastoma from patient registry data set (PRiDe)	PRiDe TTFields treatment (n=457)	EF-11 TTFields treatment (n=120)		
Survival ^g				
1-year survival	44 %	20 %		
2-year survival	30 %	9 %		

Table 1. (Continued)

Phase III trial for newly diagnosed glioblastoma interim analysis ^a Prognostic factors, median overall survival ^b Number of prior recurrences	TTFields treatment + temozolomide	Temozolomide alone	Hazard ratio	P
First recurrence versus Second recurrence	20 months 8.5 months, HR=0.6 (95 % CI 0.4–0.9), P=0.03			
Third to fifth recurrence	4.9 months, HR=0.3 (95 % CI 0.2–0.5), P<0.01			
Compliance <75 % versus ≥75 %	4.0 months 13.5 months, HR=0.4 (95 % CI 0.3–0.6), P<0.01			
Karnofsky performance status 90–100 versus 70–90	14.8 months 7.7 months, HR=0.6 (95 % CI 0.4–0.9), P<0.01			
10–60	6.1 months, HR=0.4 (95 % CI 0.2–0.6), P<0.01			
Prior bevacizumab use No versus Yes	13.4 months 7.2 months, HR=0.5 (95 % CI 0.4–0.7), P<0.01			
Prior debulking surgery No versus Yes	8.9 months 9.8 months, HR=1.1 (95 % CI 0.8–1.5), P=0.79			

^aStupp R, Wong E, Scott C, et al. Neuro-Oncol 2014;16(Suppl 5):v167^bStupp R, Wong ET, Kanner AA, et al. Eur J Cancer 2012;48:2192–2202^cKanner AA, Wong ET, Villano JL, et al. Semin Oncol 2014;41(Suppl 6):S25–S34^dVymazal J, Worrig ET. Semin Oncol 2014;41(Suppl 6):S14–S24^eWong ET, Lok E, Swanson KD, et al. Cancer Med 2014;3:592–602^fLacouture ME, Davis ME, Elzinga G, et al. Semin Oncol 2014;41(Suppl 4):S1–S14^gMrugala MM, Engelhard HH, Tran DD, et al. Semin Oncol 2014;41(Suppl 6):S4–S13

The most common toxicity associated with the device was grade 1 or 2 scalp irritation at a rate of 16 %, but none had severity of grade 3 or 4. The scalp irritation can be managed by applying topical corticosteroid and by shifting of the arrays slightly during each array exchange [20]. The most important advantage associated with the TTFields therapy device, when compared to chemotherapy, is that it has far fewer grade 2 or greater hematological toxicities, 3 versus 17 %, respectively, and fewer adverse gastrointestinal events, 4 versus 17 %, respectively.

Analysis of quality of life demonstrated that patient treated with the device had better cognitive and emotional functions than those treated with chemotherapy while appetite loss, constipation, diarrhea, fatigue, nausea, vomiting, and pain were more often seen in patients treated with chemotherapy. Based on the equivalent efficacy results and the lack of serious toxicities, the TTFields therapy device was approved by US FDA on April 8, 2011 for the treatment of recurrent glioblastoma.

Post hoc analysis showed that a higher proportion of responders had secondary glioblastoma than nonresponders [21••]. Five of the 14 responders (36 %) treated with TTFields monotherapy had prior low-grade histology while none of the seven responders (0 %) treated with the best physician's choice chemotherapy did.

The analysis also showed that responders used less dexamethasone than nonresponders [21••]. In the TTFields therapy cohort, the median daily dexamethasone dose used was 1.0 mg for responders versus 5.2 mg for nonresponders ($P=0.0019$) and the median cumulative dexamethasone dose was 7.1 mg for responders versus 261.7 mg for nonresponders ($P<0.0001$). In the best physician's choice chemotherapy cohort, the median daily dexamethasone dose used was 1.2 mg for responders versus 6.0 mg for nonresponders ($P=0.0041$) and the median cumulative dexamethasone dose was 348.5 mg for responders versus 242.3 mg for nonresponders ($P=0.9520$). These data suggest that concurrent dexamethasone use may influence the efficacy of TTFields therapy.

TTFields therapy as used in clinical practice

Patients who received treatment from the TTFields device in clinical practice may have different clinical characteristics and outcomes from those who participated in the registration trial. To determine whether or not this is the case, a patient registry dataset (PRiDe) was developed in an effort to capture clinical practice data pertaining to the use of TTFields therapy. At the time of publication, this dataset included 457 patients from 91 treatment centers in the USA [22•].

The median OS was 9.6 months among patients treated in PRiDe as compared to 6.6 months in the TTFields monotherapy arm in the phase III trial while the 1-year OS rate was also longer at 44 % as compared to 20 %, respectively [6, 22•]. It is important to note that some patients in PRiDe may have used other treatments, such as conventional cytotoxic chemotherapy, bevacizumab, or even alternative medicine, in conjunction with TTFields therapy, but this aspect of treatment was not adequately captured because this dataset is from a registry.

About 33 % of patients at their first glioblastoma recurrence used TTFields therapy as compared to only 9 % in the registration phase III clinical trial [22•].

Favorable prognostic factors for patient survival include treatment with TTFields therapy at first or second relapses versus third or later recurrences, as well as no prior bevacizumab use [22•].

TTFields therapy for newly diagnosed glioblastoma

TTFields therapy is currently being tested in a randomized phase III clinical trial for subjects with newly diagnosed glioblastoma (NCT0916409). The goal of this study is to compare the efficacy of TTFields plus adjuvant temozolomide versus adjuvant temozolomide alone by randomizing the subjects to the respective treatment arms in a 2:1 fashion, after the completion of initial treatment with radiation and concomitant daily temozolomide [16]. The primary endpoint is progression-free survival, and the secondary endpoints are overall survival, progression-free survival at 6 months, survival at 1 and 2 years, as well as quality of life assessment. So far, all 700 pre-specified subjects have been enrolled and randomized.

In a pre-specified interim analysis of the first 315 subjects after a minimum follow-up of 18 months, the intent-to-treat cohort received TTFields plus temozolomide ($n=210$) had a longer progression-free survival than the cohort treated with temozolomide alone ($n=105$), median 7.1 (95 % CI 5.9–8.2) months versus 4.0 (95 % CI 3.0–4.3) months (HR=0.63, Log rank $P=0.0014$). The median overall survival also favors the TTFields plus temozolomide group, 19.6 (95 % CI 16.5–24.1) months versus 16.6 (95 % CI 13.5–19.1) months, respectively (HR=0.75, Log rank $P=0.034$), as well as the per protocol population that started the second cycle of treatment, 20.5 (95 % CI 16.5–24.1) months ($n=196$) versus 15.5 (95 % CI 13.5–19.1) months ($n=84$), respectively (HR=0.67, Log rank $P=0.0042$).

There were no unexpected adverse events between the TTFields plus temozolomide and the temozolomide alone cohorts, and respective grade 3 and 4 hematological toxicities (12 versus 9 %), gastrointestinal disorders (5 versus 2 %), and convulsions (7 versus 7 %) were similar. Scalp reaction, however, was more common in the device-treated cohort, 49 % for grades 1 and 2 as well as 7 % for grade 3 and 4 toxicities, than the temozolomide-only cohort, 5 % for grade 1 and 2 toxicities as well as 5 % for grade 3 and 4 toxicities.

The follow-up of the remaining trial subjects will most likely mature in another year such that final data from the trial will be available by the end of 2016.

Additional investigational studies of TTFields therapy for the central nervous system or other malignancies

Combinations with TTFields are being studied in patients with recurrent glioblastoma including bevacizumab (NCT01894061) and bevacizumab together with hypofractionated stereotactic irradiation (NCT01925573).

TTFields therapy is currently being investigated in patients with other types of central nervous system malignancies, including its use for recurrent atypical and anaplastic meningiomas (NCT01892397), as well as in those patients with 1–5 brain metastases from non-small cell lung cancer (NCT01755624).

TTFields therapy is also being investigated in systemic malignancies, including its use in combination with gemcitabine for advanced pancreatic adenocarcinoma (NCT01971281), in combination with paclitaxel in recurrent ovarian carcinoma (NCT02244502), as well as in combination with pemetrexed and cisplatin or carboplatin for malignant pleural mesothelioma (NCT02397928).

Compliance with Ethics Guidelines

Conflict of Interest

Eric T Wong received an unrestricted grant from Novocure for the investigation of the cell biology effects of TTFields; participated in the registration trial for recurrent glioblastoma and the PRiDe dataset; and has received sponsored clinical research through grants from AngioChem, AstraZeneca, Cephalon, Eli Lilly, Northwest Biotherapeutics, Novartis, Pfizer, and Plexxikon.

Edwin Lok declares that he has no conflict of interest.

Kenneth D. Swanson received an unrestricted grant from Novocure for the investigation of the cell biology effects of TTFields and has also received a reimbursement for travel expenses for training on use of laboratory equipment and an honorarium for a lecture at Novocure headquarters to present the results of basic research studies.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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This study demonstrated that septin 2, 6 and 7

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- This paper documented the pattern of TTFields therapy usage in clinical practice.

BJC

Cancer Research UK

Keywords: dexamethasone; glioblastoma; NovoTTF-100A; tumour immunology; chemotherapy

Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma

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Background: Patients with recurrent glioblastoma have a poor outcome. Data from the phase III registration trial comparing tumour-treating alternating electric fields (TTFields) vs chemotherapy provided a unique opportunity to study dexamethasone effects on patient outcome unencumbered by the confounding immune and myeloablative side effects of chemotherapy.

Methods: Using an unsupervised binary partitioning algorithm, we segregated both cohorts of the trial based on the dexamethasone dose that yielded the greatest statistical difference in overall survival (OS). The results were validated in a separate cohort treated in a single institution with TTFields and their T lymphocytes were correlated with OS.

Results: Patients who used dexamethasone doses >4.1 mg per day had a significant reduction in OS when compared with those who used ≤ 4.1 mg per day, 4.8 vs 11.0 months respectively ($\chi^2 = 34.6$, $P < 0.0001$) in the TTField-treated cohort and 6.0 vs 8.9 months respectively ($\chi^2 = 10.0$, $P < 0.0015$) in the chemotherapy-treated cohort. In a single institution validation cohort treated with TTFields, the median OS of patients who used dexamethasone >4.1 mg per day was 3.2 months compared with those who used ≤ 4.1 mg per day was 8.7 months ($\chi^2 = 11.1$, $P = 0.0009$). There was a significant correlation between OS and T-lymphocyte counts

Conclusions: Dexamethasone exerted profound effects on both TTFields and chemotherapy efficacy resulting in lower patient OS. Therefore, global immunosuppression by dexamethasone likely interferes with immune functions that are necessary for the treatment of glioblastoma.

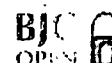
Patients with recurrent glioblastoma have limited treatment options. Bevacizumab is a standard of care for patients with recurrent glioblastoma and it produces an objective response rate of 25–60% (Wong *et al*, 2011). However, its ability to prolong patient overall survival (OS) is questionable (Iwamoto and Fine, 2010; Reardon *et al*, 2012). The NovoTTF-100A device is another FDA-approved treatment for recurrent glioblastoma that works by emitting tumour-treating alternating electric fields (TTFields) via two pairs of transducer arrays placed orthogonally on the scalp and acts to perturb tumour cells during mitosis (Kirson *et al*, 2004, 2007; Gera *et al*, 2015). Preclinical data show that cells affected by TTFields exhibit violent plasma membrane blebbing that disrupts the normal spatial ordering of the mitotic chromosomes.

This results in asymmetric chromosome segregation and aneuploidy owing to defects in cytokinesis and aberrant mitotic exit. Furthermore, these cells also exhibit signs of stress that include elevated cell surface expression of calreticulin, which makes them more readily detectable by phagocytic immune cells, facilitating an immune response against the tumour (Lee *et al*, 2013). Importantly, the NovoTTF-100A device was demonstrated to possess equivalent efficacy when compared with best physician's choice (BPC) chemotherapy in the registration phase III clinical trial, but without the myeloablative toxicities associated with systemic chemotherapies that may cause secondary systemic infection or interference with immune effector function (Vecht *et al*, 1994; Hughes *et al*, 2005; Stupp *et al*, 2012; Fonkem and Wong, 2012).

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More recently, a prespecified interim analysis of the results from an upfront phase III clinical trial in newly diagnosed glioblastoma patients, comparing NovoTTF-100A plus adjuvant temozolomide vs adjuvant temozolomide alone, revealed significantly improved patient outcome with a respective progression-free survival of 7.1 vs 4.0 months and OS of 19.6 vs 16.6 months (Stupp *et al*, 2014). Compared with newly diagnosed glioblastomas, patients with recurrent glioblastoma likely have several factors that led to a worse outcome, including clonal evolution of the tumour, evasion of the immune system and reduction of immune competence because of prior exposure to chemotherapy.

Dexamethasone is commonly used to treat neurologic symptoms caused by the glioblastoma (Vecht *et al*, 1994). However, it also has a plethora of systemic toxicities, including gastrointestinal haemorrhage with or without perforation, infection, and hyperglycaemia (Heimdal *et al*, 1992). Although dexamethasone has not been shown to interfere directly with the efficacy of treatments against glioblastoma, there is emerging evidence from both preclinical and clinical data in other malignancies to suggest that dexamethasone may affect the patient's antitumour immunity. First, although the immune system has evolved multiple mechanisms to recognise and eliminate neoplastic cells (Senovilla *et al*, 2013), tumours emerge within the patient when they escape immune surveillance (Mittal *et al*, 2014). At this point, the tumour further subverts the immune system by eliciting normal wound healing and tissue remodelling responses, whereas promoting a state of immune privilege within the tumour microenvironment (Schreiber *et al*, 2011). In this setting, dexamethasone may potentiate existing local immunosuppression via global induction of I κ B α and inhibition of NF- κ B activity in lymphocytes, resulting in global immunosuppression (Auphan *et al*, 1995). Second, dexamethasone can lower the number of CD4⁺ lymphocytes in newly diagnosed patients with glioblastoma treated with radiation alone or in combination with temozolomide, and this attenuated CD4⁺ lymphocyte count is associated with increased infections and decreased survival (Hughes *et al*, 2005; Grossman *et al*, 2011). Lastly, recent clinical trial data have shown that there were more systemic and central nervous system responders to ipilimumab, an immune checkpoint inhibitor, in the cohort taking no dexamethasone as compared with the cohort taking dexamethasone, suggesting that dexamethasone interferes with the efficacy of ipilimumab (Margolin *et al*, 2012).

In this paper, we present evidence that immune suppression by dexamethasone markedly interferes with the clinical efficacy of two disparate therapies for recurrent glioblastoma: electric field-based therapy delivered by the NovoTTF-100A as well as conventional chemotherapies. Unlike prior clinical trials, the cohort treated with TTField monotherapy offered us an opportunity to study unambiguously the effect of dexamethasone on patient survival unencumbered by concurrent chemotherapies that suppress the immune system. We also present data that strongly support a role for immune competence in effecting TTField treatment by analysing T-cell subsets measured in a separate cohort of patients for validation.

PATIENTS AND METHODS

Patients. Subjects signed informed consent from their respective treating institutions before participation in the phase III trial comparing NovoTTF-100A vs BPC chemotherapy (Fonkem and Wong, 2012; Stupp *et al*, 2012). A *post hoc* analysis of the dexamethasone effect on the two cohorts was performed based on anonymised data obtained from the sponsor, from whom the corresponding author had full access to the primary data. The outcome of the analysis was then validated retrospectively, under

an institutional review board-approved protocol from Dana Farber/Harvard Cancer Center (protocol no. 12-519), using a separate cohort of patients who were treated with NovoTTF-100A and bevacizumab at Beth Israel Deaconess Medical Center.

Statistical analysis. Statistical analyses were performed by using R statistics base package (<http://www.r-project.org>) and its libraries. Two-tailed Wilcoxon's rank-sum test with continuity correction was used to determine whether two independent groups of data were statistically different from each other. A modified binary search algorithm (Knuth, 1971; Tøndel *et al*, 2002), written in R, was used to iteratively partition data in both two and three dimensions. The Loess local nonparametric polynomial regression was used to perform curve fitting of the OS as a function of dexamethasone dose (Cleveland, 1979; Shipley and Hunt, 1996; Cleveland and Loader, 1996) and OS was analyzed using Kaplan-Meier statistics (Kaplan and Meier, 1958).

RESULTS

Effect of dexamethasone on TTField therapy and BPC chemotherapy. Our previous *post hoc* analysis of responders in the phase III trial demonstrated that responders to TTField therapy required significantly lower doses of dexamethasone compared with non-responders (Wong *et al*, 2014). We therefore investigated further whether there was a threshold dose of dexamethasone that affected outcome within the entire trial population. Using an unsupervised binary partitioning algorithm (Knuth, 1971; Tøndel *et al*, 2002), we stratified the TTField therapy cohort based on the dexamethasone dose that yielded the greatest statistical difference in median OS. The results revealed that subjects who used >4.1 mg per day dexamethasone ($n=64$) exhibited a significantly shortened median OS of 4.8 months (95% confidence interval (CI): 3.9–6.0) vs those who used ≤ 4.1 mg per day ($n=56$), with a median OS of 11.0 months (95% CI: 8.8–16.6) ($\chi^2=34.6$, $P<0.0001$; Figure 1A). We then used the same dexamethasone cutoff to stratify control patients in the BPC chemotherapy cohort and observed a similar, albeit less robust, dichotomisation, with a respective median OS of 6.0 months (95% CI: 3.5–8.3) ($n=54$) vs 8.9 months (95% CI: 7.2–16.1) ($n=63$) ($\chi^2=10.0$, $P=0.0015$; Figure 1B) for those receiving >4.1 vs ≤ 4.1 mg per day of dexamethasone, respectively. There are two potential explanations for these results: either patients with larger, more aggressive tumours required a higher dose of dexamethasone for symptom control or doses of dexamethasone >4.1 mg per day interfered with both therapeutic interventions used in this trial. However, tumour size did not differ statistically between patient cohorts that used dexamethasone at either >4.1 or ≤ 4.1 mg per day (Figures 1C and D). Therefore, factors other than tumour size influence the OS of subjects receiving high vs low doses of dexamethasone.

To further investigate the effect of dexamethasone on patient outcome, we compared the survival characteristics of the cohort treated with TTField therapy to the one treated with BPC chemotherapy in the respective dexamethasone dosage groups. First, we compared the two treatment groups when the dosage of dexamethasone used was ≤ 4.1 mg per day. Although the two OS curves overlapped ($\chi^2=0.9$, $P=0.3510$; Figure 2A), we detected a marked separation between these two curves at time points less than the median OS. Indeed, when we compared the survival curves of the two cohorts for subjects who used dexamethasone ≤ 4.1 mg per day and possessed survival times of less than the median OS, we found a significant difference between the two subgroups, with a median OS of 6.6 (range 1.4–10.1) months for the TTField-treated subgroup ($n=31$) vs 3.9 (range 0.0–8.6) months for the BPC chemotherapy-treated subgroup ($n=40$) ($P=0.0015$; Figure 2C). However, for subjects who lived longer

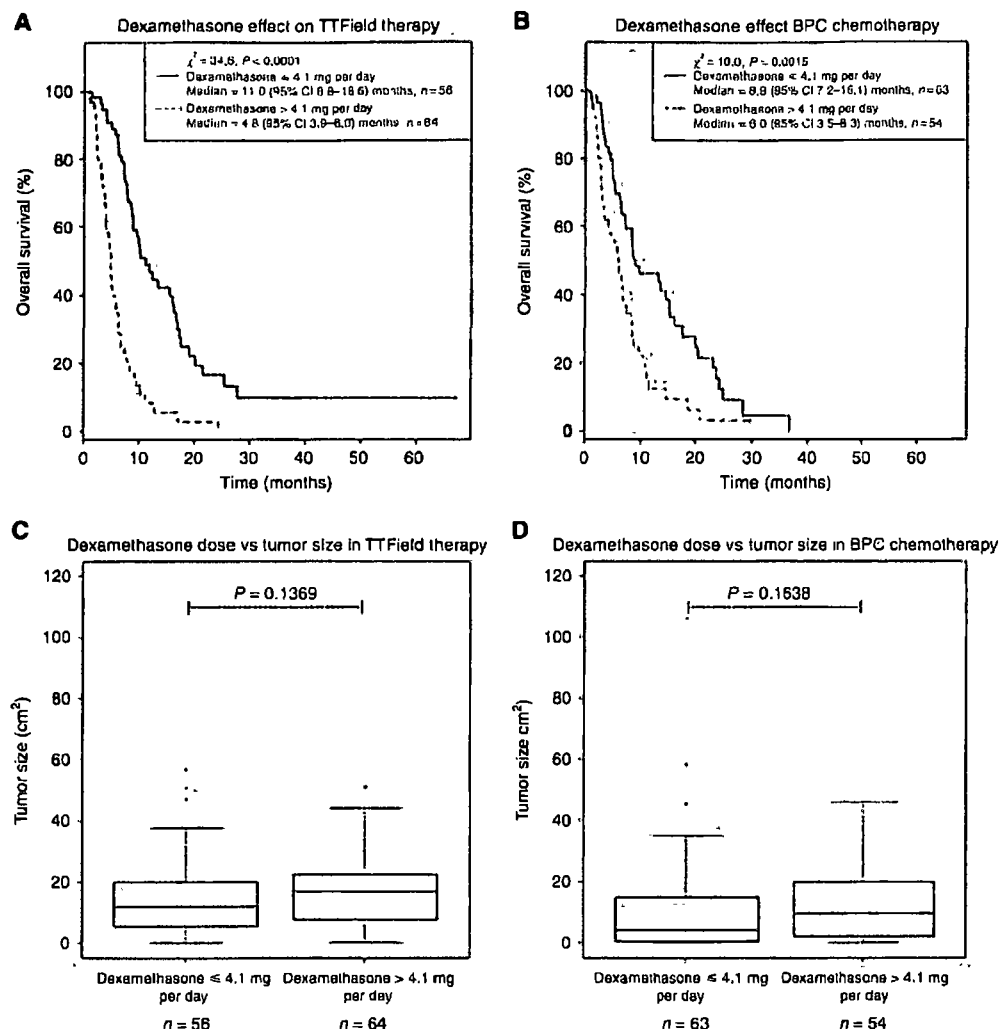


Figure 1. Kaplan-Meier OS and tumour size with respect to dexamethasone requirement of ≤ 4.1 vs > 4.1 mg per day from subjects enrolled in the phase III trial comparing TTField therapy vs BPC chemotherapy. (A) Subjects enrolled in the TTField treatment arm taking dexamethasone ≤ 4.1 (solid blue) vs > 4.1 (dashed blue) mg per day, which was determined by an unsupervised binary partitioning algorithm. Subjects who used ≤ 4.1 mg per day of dexamethasone ($n = 56$) had a median OS of 11.0 months (95% CI: 8.8–16.6) as compared with those who used > 4.1 mg per day ($n = 64$) had a median OS of 4.8 months (95% CI: 3.9–6.0) ($\chi^2 = 34.6, P < 0.0001$). (B) Subjects enrolled in the BPC chemotherapy arm taking dexamethasone ≤ 4.1 (solid red) vs > 4.1 (dashed red) mg per day was determined by the same unsupervised binary partitioning algorithm. Subjects who used ≤ 4.1 mg per day of dexamethasone ($n = 63$) had a median OS of 8.9 months (95% CI: 7.2–16.1) as compared with those who used > 4.1 mg per day ($n = 54$) had a median OS of 6.0 months (95% CI: 3.5–8.3) ($\chi^2 = 10.0, P = 0.0015$). (C) Box-and-whisker plot of bidimensional tumour size in the TTField therapy cohort that received dexamethasone ≤ 4.1 vs > 4.1 mg per day. Subjects who took dexamethasone ≤ 4.1 mg per day ($n = 56$) had a median tumour size of 11.9 (range 0.0–56.7) cm^2 as compared with those who used > 4.1 mg per day ($n = 64$) had a median tumour size of 16.8 (range 0.3–51.0) cm^2 ($P = 0.1369$). (D) Box-and-whisker plot of bidimensional tumour size in the BPC chemotherapy cohort that received dexamethasone ≤ 4.1 vs > 4.1 mg per day. Subjects who took dexamethasone ≤ 4.1 mg per day ($n = 63$) had a median tumour size of 4.2 (range 0.0–11.2) cm^2 as compared with those who used > 4.1 mg per day ($n = 54$) had a median tumour size of 9.6 (range 0.0–46.0) cm^2 ($P = 0.1638$).

than the median OS, there was no difference in the OS curves, with a median OS of 16.7 (range 11.0–66.9) months for the TTField-treated subgroup ($n = 25$) vs 16.8 (range 8.9–36.7) months for the BPC chemotherapy-treated subgroup ($n = 23$) ($P = 0.5773$; Figure 2E). In contrast, among subjects who received high dexamethasone doses of > 4.1 mg per day, the overlapping OS curves ($\chi^2 = 1.5, P = 0.2240$; Figure 2B) appeared to diverge for the subjects whose survival were greater than the median OS. Remarkably, the TTField-treated subgroup was worse compared with the BPC chemotherapy-treated subgroup when treated with

dexamethasone doses > 4.1 mg per day, with a respective median OS of 6.7 (range 4.8–24.3) months ($n = 29$) vs 8.7 (range 6.0–29.6) months ($n = 22$) ($P = 0.0097$; Figure 2D). However, for subjects whose survival were less than the median OS and used > 4.1 mg per day dexamethasone, there was no difference between the TTField-treated and the BPC chemotherapy-treated subgroups, with the former having a median OS of 3.0 (range 0.8–4.5) months ($n = 35$) as compared with the latter having a median OS of 2.8 (range 0.2–5.8) months ($n = 32$) ($P = 0.8456$; Figure 2E). Collectively, the data in Figures 2C and D indicate that the extent

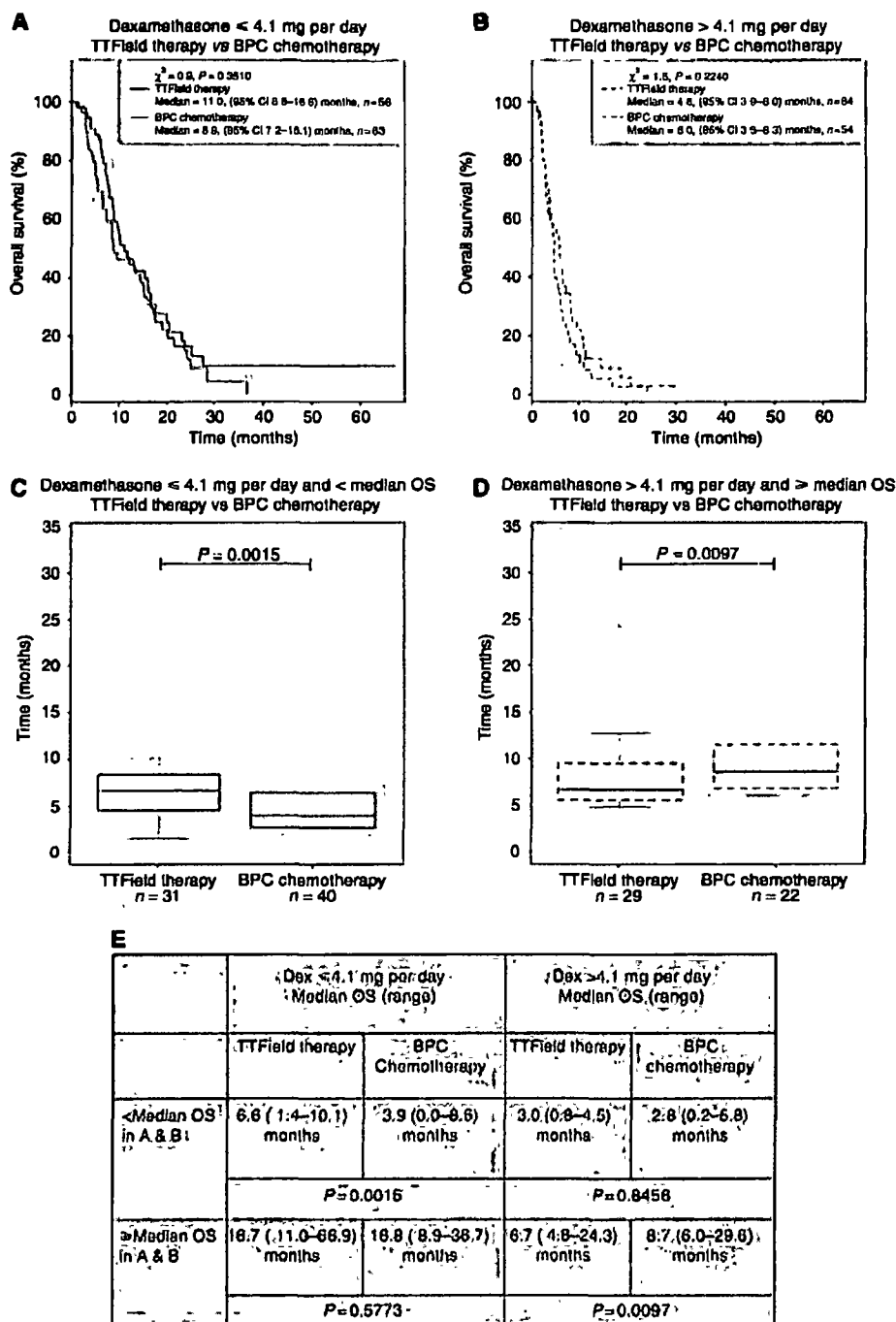


Figure 2. Comparison of OS in subjects treated with TTField therapy vs BPC chemotherapy segregated by dexamethasone usage.

(A) Comparison of subjects using dexamethasone ≤ 4.1 mg per day in both TTField therapy (blue) and BPC chemotherapy (red) arms. (B) Comparison of subjects using dexamethasone > 4.1 mg per day in both TTField therapy and BPC chemotherapy arms. (C) Box-and-whisker plot of OS between TTField vs BPC chemotherapy-treated subjects using ≤ 4.1 mg per day of dexamethasone and $<$ the median OS in (A). The median OS was 6.6 months (range 1.4–10.1) for TTField-treated subjects ($n = 31$) vs 3.9 months (range 0.0–8.6) for BPC chemotherapy-treated subjects ($n = 40$) ($P = 0.0015$). (D) Box-and-whisker plot of OS between TTFields vs BPC chemotherapy-treated subjects using > 4.1 mg per day of dexamethasone and \geq the median OS in (B). The median OS was 6.7 months (range 4.8–24.3) for TTField-treated subjects ($n = 29$) vs 8.7 months (range 6.0–29.6) for BPC chemotherapy-treated subjects ($n = 22$) ($P = 0.0097$). (E) Median OS, range, and P -values for the four subgroups: (i) dexamethasone ≤ 4.1 mg per day and $<$ median OS in (A), (ii) dexamethasone > 4.1 mg per day and $<$ median OS in (B), (iii) dexamethasone ≤ 4.1 mg per day and \geq median OS in (A), and (iv) dexamethasone > 4.1 mg per day and \geq median OS in (B).

of dexamethasone exposure not only predicted treatment efficacy but also strongly suggest that TTField therapy is superior to BPC chemotherapy in the setting of low dexamethasone usage. However, under the influence of higher dexamethasone usage, the benefit of TTField therapy appeared to be negated to a greater extent when compared with BPC chemotherapy as if TTField-treated subjects were not provided with any therapy at all.

Dose-dependent effect of dexamethasone on treatment efficacy.

We next asked whether or not dexamethasone has a dose-dependent influence on treatment efficacy by analysing the entire dose spectrum used in the trial. We partitioned the TTField-treated cohort using a dexamethasone dose cutoff from 0.0 to 37.0 mg per day, plotted the respective median OS of the groups at \leq cutoff or $>$ cutoff vs successive dexamethasone dosages, and fitted the data with the best curves using the nonparametric Loess local polynomial regression (Figure 3) (Cleveland, 1979; Cleveland and Loader, 1996; Shipley and Hunt, 1996). In addition, we plotted the log-rank P -values of the dichotomised groups in each successive dexamethasone dosage and found two nadir P -values of 0.00000008 and 0.00002524 corresponding to dexamethasone doses of 4.1 and 7.8 mg per day, respectively. We observed that there was decremental OS starting at a dexamethasone dose of 4.1 mg per day and, with successive increases of dexamethasone, reached an inflection point at 7.8 mg per day, after which the rate of OS decreased slowly (Figure 3A).

We also performed the same dose-dependent analysis of dexamethasone in the BPC chemotherapy-treated cohort and found a nadir P -value of 0.00163291 at 3.3 mg per day and another of 0.00011858 at 7.5 mg per day. Similarly, the best-fit curve derived in Figure 3B also suggests that the dexamethasone dose near 4 mg per day may also represent a point at which decremental OS can be observed with successive increases in dexamethasone dosage. This progressive decrement in OS occurred with successive increases of dexamethasone until an inflection point is observed at a dose near 7.5 mg per day, after which the rate of OS decreased slowly. Taken together, both cohorts experienced interference from dexamethasone at a dose near 4.0 mg per day and a maximal effect was observed near 7.5 mg per day.

Validation of the dexamethasone effect on TTField-treated patients from a single institution. We next proceeded to validate the observed dexamethasone effect on patient outcome within the trial by retrospectively analysing our own single-institution cohort. From November 2012 to February 2014, we treated 38 patients (Table 1) using TTField monotherapy as treatment or in combination with bevacizumab, whereas dexamethasone usage was aggressively reduced. Three patients who were referred specifically to our institution did not receive TTField therapy because of patient choice of other treatments, severe medical comorbidities, or advanced intracranial disease that was deemed more suitable for hospice care. Among the remaining 35 patients, their median OS was 4.3 months (95% CI: 3.5–8.7). To properly compare this cohort with the subjects enrolled in the phase III trial, we included only those with a KPS ≥ 70 or greater ($n = 23$) in our validation set. This sub-population exhibited a median OS of 8.0 months (95% CI: 3.8–13.8) compared with 3.2 months (95% CI: 1.4–NA) for the remaining patients with a KPS < 70 ($n = 12$) ($\chi^2 = 8.5$, $P = 0.0035$; Figure 4A). We then applied a cutoff of dexamethasone 4.1 mg per day as was found in our previous binary partitioning analysis. Patients who used dexamethasone ≤ 4.1 mg per day had a significantly longer OS compared with those who used > 4.1 mg per day, with a median OS of 8.7 months (95% CI: 6.7–NA) ($n = 19$) vs 3.2 months (95% CI: 1.2–NA) ($n = 4$), respectively ($\chi^2 = 11.1$, $P = 0.0009$; Figure 4B). Although our single-institution cohort has fewer patients compared with the cohorts in the phase III trial, we nevertheless observed a robust segregation of OS in the patient groups, validating the previously observed effect of dexamethasone on patient outcome.

Comparison of patients within the validation cohort with a KPS ≥ 70 and dexamethasone usage ≤ 4.1 mg per day ($n = 19$) to the phase III TTField therapy cohort who used dexamethasone ≤ 4.1 mg per day ($n = 56$, from Figure 2A) revealed no statistical difference between the two groups, with a median OS of 8.7 months (95% CI: 6.7–NA) vs 11.0 months (95% CI: 8.8–16.6), respectively ($\chi^2 = 2.1$, $P = 0.1520$; Figure 4C). We next asked whether important prognostic factors within our cohort varied relative to patients within the phase III cohort by examining the possible effects of age and tumour size. The median age of our

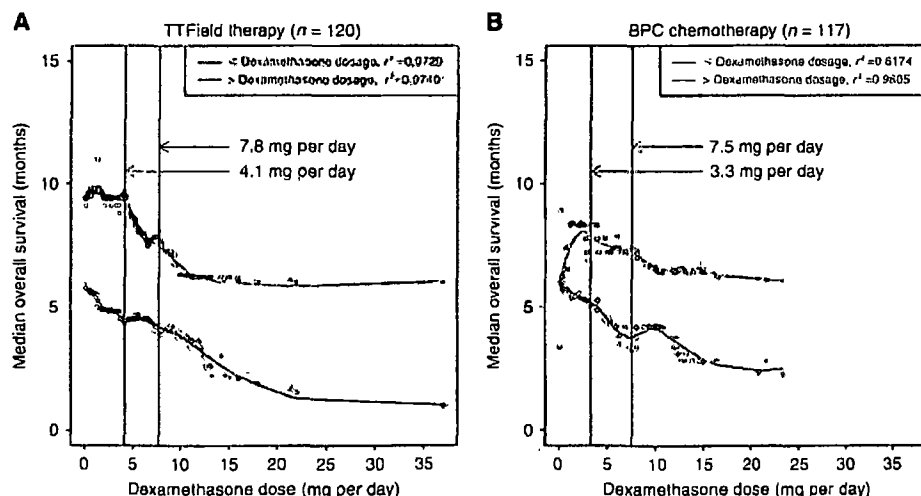


Figure 3. Loess local polynomial regression of median OS vs dexamethasone dose. Dexamethasone was treated as a discrete variable successively and the median OS was plotted for the group \leq (green) and $>$ (blue) compared with the variable dosage of dexamethasone. Curve fitting was performed using the Loess local polynomial regression. (A) In the TTField therapy cohort ($n = 120$), there was decremental OS from 4.1 mg per day that reached an inflection point at 7.8 mg per day, after which the rate of OS decrease slowed. (B) In the BPC chemotherapy cohort ($n = 117$), there was decremental OS from 3.3 mg per day that reached an inflection point at 7.5 mg per day, after which the rate of OS decrease slowed.

Table 1. Patient characteristics in the validation cohort and the NovoTTF-100A cohort in phase III trial

Patient characteristics	Validation cohort (n = 35)	NovoTTF-100A cohort (n = 120)	P-value
Age (range)	57 (30–77) years	54 (24–80) years	
Gender			
Male	22 (63%)	92 (77%)	
Female	13 (37%)	28 (23%)	
Karnofsky performance status			
Median	70 (range 50–90)	80 (range 50–100)	
Tumour size, bidimensional			
T1 Gad, median (range) (cm ²)	12.2 (0.3–40.6)	14.2 (0.0–56.7)	0.6178
FLAIR, median (range) (cm ²)	35.2 (7.0–90.9)	N/A	
Dexamethasone dose			
Median (range) (mg per day)	3.0 (0.0–15.0)	4.7 (0.0–37.5)	
Absolute T-cell subsets			
CD3, median (range) (cells per mm ³)	733 (70–1458)	N/A	
CD4, median (range) (cells per mm ³)	414 (25–788)	N/A	
CD8, median (range) (cells per mm ³)	302 (44–1039)	N/A	
Prior therapy			
First recurrence	6 (17%)	11 (9%)	
Second recurrence	10 (29%)	58 (48%)	
Third recurrence	19 (54%)	51 (43%)	
Prior bevacizumab	25 (71%)	23 (19%)	
Outcome			
Overall survival, median (months)	4.3 (95% CI: 3.5–8.7)	7.1 (95% CI: 6.1–8.8)	0.0468

Abbreviations: CI = confidence interval; FLAIR = fluid-attenuated inversion recovery; Gad = gadolinium; N/A = not applicable; TTF = tumour-treating alternating electric field.

cohort was 57 (range 30–77) years and it is not different from the median age of 54 (range 24–80) years in the TTField-treated cohort from the phase III trial (Stupp *et al*, 2012). Average tumour size in our cohort as measured by gadolinium-enhanced T1-weighted MRI showed a median bidimensional measurement of 12.2 (range 0.30–40.6) cm², which is similar to the median bidimensional measurement of 14.2 (0.0–56.7) cm² in the TTField-treated phase III cohort ($P = 0.6178$; Table 1). However, 15 of 23 patients (65%) were already on bevacizumab before their neuroimaging studies, possibly interfering with tumour measurement because bevacizumab can reduce vascular permeability in tumours causing decreased gadolinium enhancement (Wong and Brem, 2008). Further, blockade of vascular endothelial growth factor can promote an invasive and diffuse glioblastoma phenotype that result in tumours possessing greater size than can be measured on gadolinium-enhanced T1-weighted MRI (Norden *et al*, 2008; Lu *et al*, 2012). We therefore measured the bidimensional size of the FLAIR abnormality. Indeed, in our cohort, the median bidimensional FLAIR abnormality was 29.6 (range 7.0–60.2) cm², which is more than two times the tumour size observed on gadolinium-enhanced T1-weighted MRI in the phase III trial (Stupp *et al*, 2012). As expected, this bevacizumab effect on tumour measurement was corroborated in our entire patient cohort ($n = 38$) by the strong correlation between the size of the gadolinium-enhanced T1-weighted and FLAIR measured bidimensional tumour size among those not on bevacizumab ($r^2 = 0.7333$, $n = 10$; Supplementary Figure 1A), whereas no such correlation was seen among those on bevacizumab ($r^2 = 0.1446$, $n = 27$; Supplementary Figure 1B). Furthermore, we found that patients in our validation cohort who used dexamethasone > 4.1 mg per day ($n = 4$) had a worse outcome compared with the corresponding cohort in the phase III trial ($n = 64$), with a median OS of 3.2 months (95% CI: 1.2–NA) vs 4.8 months (95% CI: 3.9–6.0), respectively ($\chi^2 = 6.3$, $P = 0.0121$; Figure 4D). Therefore, our single-institution validation cohort, who had KPS ≥ 70 , used dexamethasone ≤ 4.1 mg per day and possessed greater tumour burden, compared favourably with those treated with TTFields therapy in the phase III trial, but those with KPS ≥ 70 but used

dexamethasone > 4.1 mg per day probably suffered from a worse outcome compared with the corresponding trial cohort.

Patient immune characteristics and TTField therapy efficacy. Dexamethasone has been associated with profound immunosuppression (Hughes *et al*, 2005; Grossman *et al*, 2011) and it may severely limit a patient's ability to mount an antitumour immune response against the glioblastoma (Zitvogel *et al*, 2008a). Our data clearly demonstrated that dexamethasone doses higher than a threshold level of 4.1 mg per day correlated with a poorer patient outcome during TTField therapy. This finding strongly suggests an immunological component behind the efficacy of this intervention and that factors required for general immune competence may have a role in predicting therapeutic outcome in our patients. We therefore analysed their CD3⁺, CD4⁺, and CD8⁺ T-lymphocyte subsets during the course of their treatment. Using the unsupervised binary partitioning approach described above for dexamethasone dose, we attempted to identify whether there was any threshold for the absolute CD3⁺, CD4⁺, or CD8⁺ T-lymphocyte count, which yielded the greatest statistical difference in OS when used to stratify our patient population. Significantly, this analysis revealed that the median OS of patients with absolute CD3⁺ ≤ 382 cells per mm³ was 2.0 months (95% CI: 1.2–NA) ($n = 7$). In contrast, the median OS of those with CD3⁺ > 382 cells per mm³ was 7.6 months (95% CI: 4.3–13.9) ($n = 22$) ($\chi^2 = 17.8$, $P < 0.0001$; Figure 5A), with the data showing that patient survival was positively correlated with the absolute numbers of CD3⁺ T lymphocytes. Similarly, we found that patients with absolute CD4⁺ ≤ 236 cells per mm³ exhibited a median OS of 2.7 months (95% CI: 1.4–NA) ($n = 9$) as compared with those with CD4⁺ > 236 cells per mm³ with a median OS of 8.0 months (95% CI: 4.6–NA) ($n = 20$) ($\chi^2 = 13.4$, $P = 0.0002$; Figure 5B). Furthermore, patients with an absolute CD8⁺ count of ≤ 144 cells per mm³ exhibited a median OS of 2.0 months (95% CI: 2.0–NA) ($n = 5$) as compared with 6.8 months (95% CI: 3.9–13.8) ($n = 24$) for those with CD8⁺ > 144 cells per mm³ ($\chi^2 = 8.1$, $P = 0.0045$; Figure 5C).

We next asked whether CD3⁺, CD4⁺, and CD8⁺ lymphocyte counts was related to the overall status of the patient's peripheral

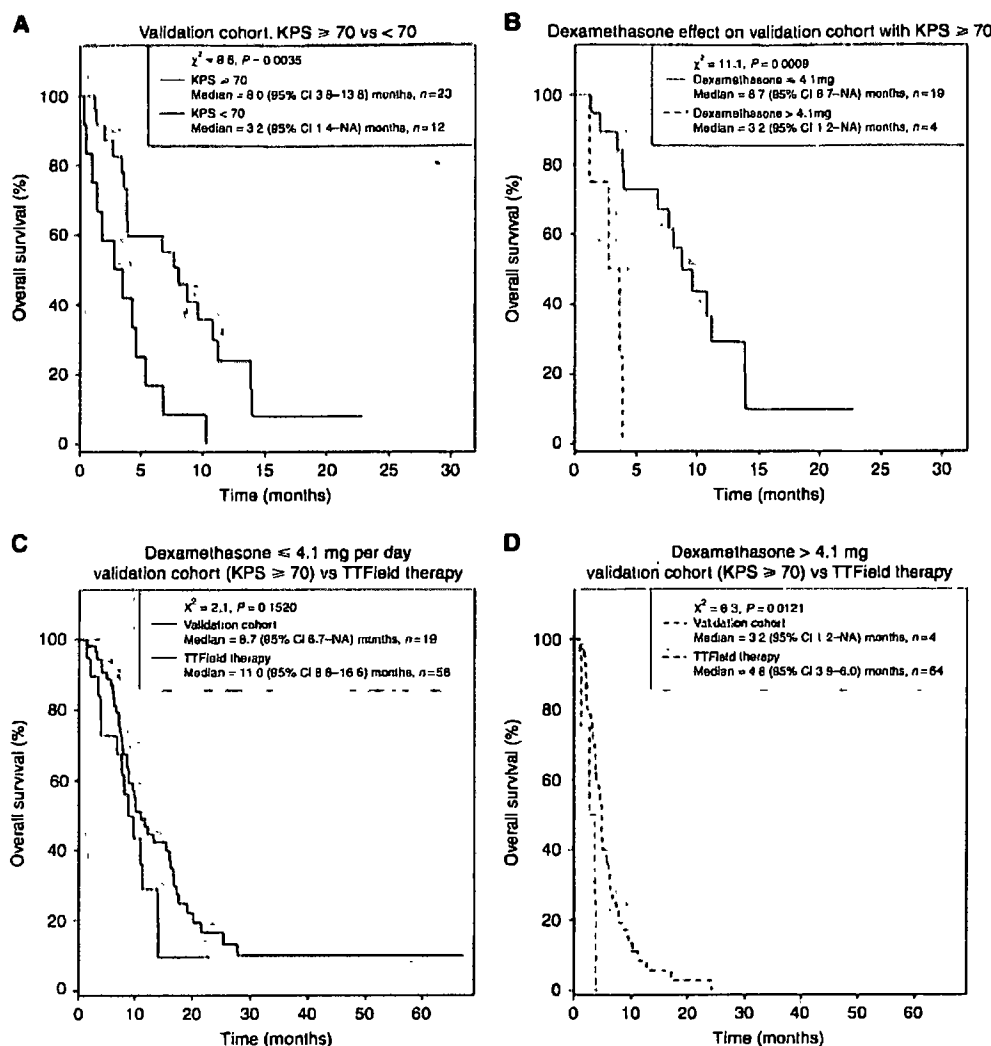


Figure 4. Kaplan-Meier estimates of survival in the validation cohort from a single institution. (A) The Kaplan-Meier survival curves for patients with KPS ≥ 70 (solid green) vs those with KPS < 70 (solid black) (B) Dexamethasone effect on the cohort with KPS ≥ 70 by comparing patients taking dexamethasone ≤ 4.1 (solid green) vs those taking > 4.1 mg per day (dashed green). (C) Comparison of the TTField-treated subjects who used ≤ 4.1 mg per day of dexamethasone in the phase III trial (from Figure 2A) vs the validation cohort with having KPS ≥ 70 and taking dexamethasone ≤ 4.1 mg per day. (D) Comparison of the TTField-treated subjects who used > 4.1 mg per day of dexamethasone in the phase III trial (from Figure 2B) vs the validation cohort with having KPS ≥ 70 and taking dexamethasone > 4.1 mg per day.

blood counts and dexamethasone requirement. As expected, there was a correlation between CD3⁺ and CD4⁺ cells ($r^2 = 0.6949$) and between CD3⁺ and CD8⁺ cells ($r^2 = 0.5001$) but not between CD4⁺ and CD8⁺ cells ($r^2 = 0.0733$). However, there was no correlation between white blood cells (WBC) and CD3⁺ cells ($r^2 = 0.0053$), WBC and CD4⁺ cells ($r^2 = 0.0023$), and WBC and CD8⁺ cells ($r^2 = 0.0032$). No correlation was also detected between platelets and CD3⁺ cells ($r^2 = 0.2576$), platelets and CD4⁺ ($r^2 = 0.2746$), and platelets and CD8⁺ ($r^2 = 0.0887$). Similarly, there was no correlation between the daily dexamethasone dose and CD3⁺ cells ($r^2 = 0.1888$), dexamethasone and CD4⁺ cells ($r^2 = 0.1531$), and dexamethasone and CD8⁺ cells ($r^2 = 0.0451$). Taken together, CD3⁺, CD4⁺, and CD8⁺ lymphocyte counts appear to be independent of the peripheral blood counts and dexamethasone dose effect. Therefore, T-lymphocyte counts may serve as an independent measure of immunocompetence in our patients and predict treatment outcome when using NovoTTF-100A.

DISCUSSION

Our previous *post hoc* analysis of responders in the phase III trial comparing NovoTTF-100A monotherapy and BPC chemotherapy for recurrent glioblastoma revealed that dexamethasone and prior low-grade glioma histology were predictors of response (Wong *et al*, 2014). Traditionally, oncologists view dexamethasone's influence on glioblastoma patients from the perspective of its antioedema effect from the tumour (Vecht *et al*, 1994), antiemetic efficacy against emetogenic chemotherapies, infections from its systemic immunosuppressive property (Vecht *et al*, 1994; Hughes *et al*, 2005), and changes in contrast enhancement on computed tomography (Chamberlain *et al*, 1988) or MRI (Ostergaard *et al*, 1999). Because dexamethasone has the potential to produce profound toxicities in patients in large part by suppressing their immune system and it is a clinically modifiable factor, we therefore extended our analysis of possible dexamethasone effect on outcome

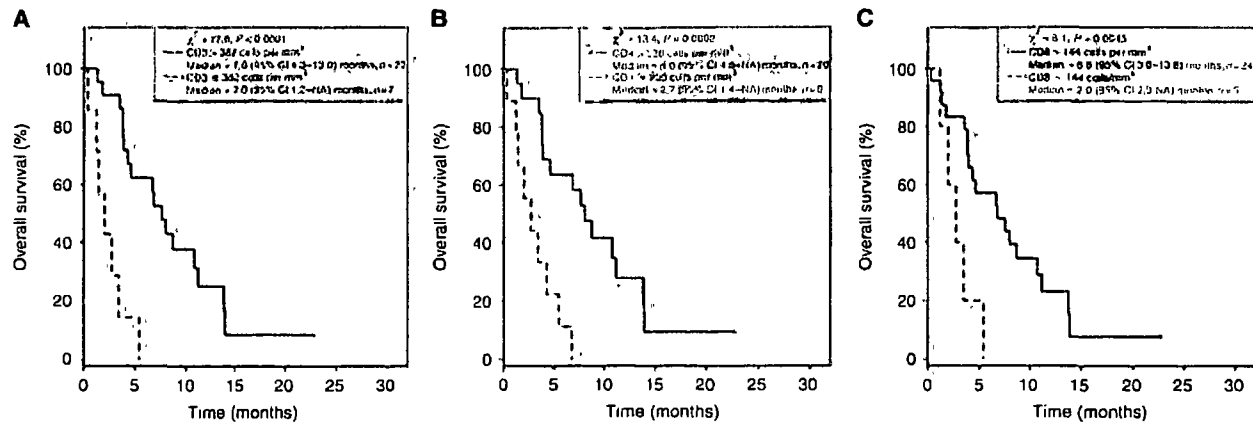


Figure 5. Wilcoxon's rank-sum test of the optimal cutoff T-lymphocyte subsets as determined by an unsupervised binary partitioning algorithm. (A) Median OS of patients with absolute CD3⁺ ≤ 382 vs > 382 cells per mm³ was 2.0 months (range 0.3–5.4) (n = 7) and 7.7 months (range 1.3–22.7) (n = 25), respectively (P = 0.0017). (B) Median OS of patients with absolute CD4⁺ ≤ 236 vs > 236 cells per mm³ was 2.7 months (range 0.3–6.7) (n = 9) and 8.0 months (range 1.3–22.7) (n = 23), respectively (P = 0.0029). (C) Median OS of patients with absolute CD8⁺ ≤ 144 vs > 144 cells per mm³ was 2.7 months (range 1.2–5.4) (n = 5) and 7.6 months (range 0.3–22.7) (n = 27), respectively (P = 0.0313).

to the entire trial cohort. In this study, we have uncovered compelling evidence that dexamethasone counteracted the therapeutic efficacy of TTFields. Further, we also found that its use negatively correlated with survival in the cohort treated with chemotherapy. Our analysis is the first to show this significant impact of dexamethasone on treatment efficacy and patient OS, which is a discrete and unequivocal endpoint in contrast to progression-free survival or response for the conduct of clinical trials for recurrent glioblastomas.

In contrast to commonly used chemotherapeutic regimens, TTField monotherapy does not exert deleterious effects on the immune system, and thus, unlike the chemotherapy-treated cohort, TTField-treated subjects did not receive concurrent immunosuppressive agents other than dexamethasone during the entire trial period. Therefore, this trial provided us with a unique opportunity to examine the interference of dexamethasone on the clinical outcome of patients without the confounding influence of cytotoxic chemotherapies. Given our previous observation that responders from this trial had low dexamethasone usage (Wong *et al*, 2014), we first asked whether we could determine a threshold of dexamethasone exposure below which a benefit in patient survival could be detected within the entire cohort. Using an unsupervised mathematical algorithm, we found that a dexamethasone dose of 4.1 mg per day produced the greatest statistical segregation of OS in the TTField-treated cohort, and subjects who received > 4.1 mg per day had a 2.3-fold decrease in median OS compared with those who used ≤ 4.1 mg per day. Notably, using this dose level to stratify the control cohort treated with BPC chemotherapy also produced a statistically significant, but less robust, OS segregation, and subjects who received > 4.1 mg per day had a 1.5-fold decrease in median OS compared with those who used ≤ 4.1 mg per day. Within both cohorts, patients exhibited a decrease in OS starting at about 4.0 mg per day, with progressive decrement until a dosage of 8.0 mg per day, above which there was no further decrease in OS. Therefore, our data indicate that dexamethasone has a generalised and profound interference on treatment efficacy regardless of whether the treatment has non-cytotoxic or cytotoxic properties on the haematopoietic system.

Our analysis strongly indicates that dexamethasone interferes with the efficacy of both TTFields and BPC chemotherapies, the latter of which consisted largely of alkylating chemotherapies. In the sub-populations taking ≤ 4.1 mg per day of dexamethasone, 31 subjects treated with TTField monotherapy exhibited a better

outcome compared with the corresponding 40 subjects treated with BPC chemotherapy. This small but statistically significant benefit occurred within the first 11 months, after which the OS of the two cohorts overlapped and the benefit from TTField therapy dissipated. In contrast, for the sub-population taking > 4.1 mg per day of dexamethasone, 29 subjects treated with TTField monotherapy exhibited a worse outcome relative to the corresponding 22 subjects treated with BPC chemotherapy. Therefore, high dexamethasone dosage appears to negate or counteract the effect of both TTField therapy and BPC chemotherapy. Because the overall trial population in the TTField-treated cohort is only 120, the benefit of treatment in the 31 (26%) subjects taking ≤ 4.1 mg per day of dexamethasone is essentially negated by the hindrance caused by the 29 (24%) patients taking > 4.1 mg per day of dexamethasone when the populations were not segregated based on dexamethasone burden. This dexamethasone interference with TTField efficacy may explained the improved outcome seen in the trial for newly diagnosed glioblastoma patients (Stupp *et al*, 2014), who were not as severely affected by treatment effects when compared with recurrent glioblastoma patients who had a longer exposure to cytotoxic chemotherapy, dexamethasone, or both.

Our data also indicate that T-lymphocyte subsets may have an important role in the outcome of our validation cohort of patients treated with TTField therapy, with prolonged OS associated with absolute CD3⁺ > 382 cells per mm³, CD4⁺ > 235 cells per mm³, and CD8⁺ > 144 cells per mm³ in an unsupervised analysis. Hughes *et al* (2005) and Grossman *et al* (2011) both showed that dexamethasone induces a drop in CD4⁺ lymphocyte count, which predisposes glioblastoma patients to infectious complications, and a CD4⁺ count < 200 cells per mm³ is associated with poor survival. However, we also noted that dexamethasone's immunosuppressive effect also blunted the therapeutic efficacy of TTField therapy and chemotherapy, probably as a result of its global interference with the patient's immune system. This notion is supported by our *in vitro* experiments, which demonstrated that cells attempting to divide in the presence of the TTFields are disrupted in mitosis during the metaphase-to-anaphase transition and experienced aberrant mitotic exit (Gera *et al*, 2015). These cells subsequently exhibited changes consistent with immunogenic cell death and thus were susceptible to immune elimination (Lee *et al*, 2011, 2013). Because subjects that received dexamethasone ≤ 4.1 mg per day in the phase III trial exhibited benefit from TTField therapy, the observed benefit is strongly consistent with an

increased immunogenicity of cells affected by TTFields. Furthermore, a number of cytotoxic chemotherapy agents, such as doxorubicin, 5-fluorouracil, and oxaliplatin, can induce either genomic or cytoplasmic stress in the tumour cell leading to immunogenic cell death (Zitvogel *et al*, 2008b). Although the extent of immunostimulatory effects of alkylators, such as lomustine, carmustine, procarbazine, and temozolomide is unknown, dacarbazine has been shown to upregulate NKG2D ligands on tumour cells and thereby target them for immune elimination by natural killer (NK) cells and CD8⁺ cytotoxic T-lymphocytes (Hervieu *et al*, 2013). Furthermore, alkylating agents have been shown to induce the secretion of ATP and HMGB1, both of which are danger signals that can activate immune responses against dying cells (Zong *et al*, 2004). Lastly, in myeloma patients, dexamethasone can severely block lenalidomide-induced NK cell activation (Hsu *et al*, 2011). Taken together, there is a strong indication from our data that the cytotoxic agents used in the trial against recurrent glioblastomas also act by inducing immune responses against the tumour and that concurrent dexamethasone usage negated this benefit.

There are a number of limitations in the interpretation of our findings. First, our data only allowed us to examine global immunosuppression in our patients but provide no means to assess local immunosuppression within the tumour microenvironment. This local suppression of immune surveillance is thought to be mediated by arginase, regulatory T cells, and myeloid-derived immunosuppressive cells (Fecci *et al*, 2006; Jacobs *et al*, 2010; Raychaudhuri *et al*, 2011). Nevertheless, removal of global immunosuppressive factors is the first step towards successful anti-glioblastoma therapy. Second, our T-lymphocyte analysis only measured cells in the adaptive immune system. However, TTField therapy and certain chemotherapy agents could potentially induce an NK cell response against the glioblastoma (Hervieu *et al*, 2013; Lee *et al*, 2013). However, the observed dexamethasone effect on absolute CD3⁺, CD4⁺, and CD8⁺ lymphocytes could also negatively influence the activation of other cytotoxic subsets such as NK cells (Hsu *et al*, 2011). Therefore, future analysis of the specific effects of dexamethasone on glioblastoma treatment would need to include the global effect on these cells.

In conclusion, dexamethasone exerted a profound interference on the therapeutic effects of both TTField therapy and BPC chemotherapies. The threshold dose at which dexamethasone was able to be used with minimal interference on these treatments was 4.1 mg per day or lower. In our validation set of TTField-treated patients, the cluster that had the longest OS had CD3⁺ > 382 cells per mm³, CD4⁺ > 236 cells per mm³, and CD8⁺ > 144 cells per mm³. Taken together, these data strongly suggest that the stimulation of immunity against the tumour operates in both of these therapeutic approaches. Future clinical trials for recurrent glioblastoma, as well as other types of brain tumours, may need to take into account the influence of dexamethasone on therapeutic outcome.

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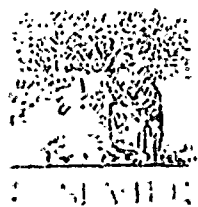
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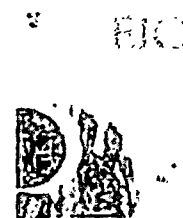
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NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality

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[†] University of Innsbruck, Austria[‡] University Hospital Zurich, Switzerland[§] Columbia University Medical Center, New York, NY, United States^{||} Lohey Clinic, Boston, MA, United States[¶] NorthShore University Health System, Evanston, IL, United States^{¶¶} Memorial Sloan Kettering Cancer Center, New York, NY, United States**KEYWORDS**

Glioblastoma
Brain tumour
Chemotherapy
Randomised trial

Abstract *Purpose:* NovoTTF-100A is a portable device delivering low-intensity, intermediate frequency electric fields via non-invasive, transducer arrays. Tumour Treatment Fields (TTF), a completely new therapeutic modality in cancer treatment, physically interfere with cell division.

Methods: Phase III trial of chemotherapy-free treatment of NovoTTF (20–24 h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. Primary end-point was improvement of overall survival.

Results: Patients (median age 54 years (range 23–80), Karnofsky performance status 80% (range 50–100) were randomised to TTF alone ($n = 120$) or active chemotherapy control ($n = 117$). Number of prior treatments was two (range 1–6). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66–1.12]; $p = 0.27$). 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% ($p = 0.13$), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, $p = 0.19$). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% ($p = 0.022$) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favoured TTF therapy in most domains.

Conclusions: This is the first controlled trial evaluating an entirely novel cancer treatment modality delivering electric fields rather than chemotherapy. No improvement in overall survival was demonstrated, however efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma. Toxicity and quality of life clearly favoured TTF.

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1. Background

Glioblastoma is the most prevalent primary malignant brain tumour in adults. Median survival with optimal therapy is only 15 months from diagnosis, and most tumours recur within 9 months of initial treatment.¹ At the time of disease recurrence, treatment options for glioblastoma patients are limited. Repeat surgery may be considered in approximately 20% of patients,^{2–4} and re-irradiation is possible in rare circumstances. For most patients chemotherapy is indicated at disease recurrence, with the choice of drug varying greatly. In the United States, bevacizumab has been provisionally approved for recurrent glioblastoma, while the European Medicines Agency (EMA) rejected the application in the absence of a controlled trial.^{5,6} Cytotoxic agents most frequently used are alkylating agents like nitrosoureas (e.g. lomustine [CCNU] or carmustine [BCNU],⁷ procarbazine⁸ or re-treatment with temozolomide.^{9,10} Response rates are below 10%, progression-free survival rates at 6 months <20%.^{7,8} In the absence of an established and satisfactory standard treatment, bevacizumab

alone and in combination with irinotecan and experimental treatments are commonly used.^{11–13}

Overall survival (OS) from recurrence is commonly short and without effective therapy rarely exceeds 3–5 months.^{14–17} In a randomised trial of repeat surgery with implantation of carmustine wafers versus placebo median survival was 6.5 versus 4.7 months.²⁰ With active therapy, a median survival of 7 months (range 5–9.2 months)^{7–10,12,13,21–24} has been reported. A recent randomised comparison of enzastaurin versus lomustine at first recurrence demonstrated a median survival of 7.1 months, with 19% of patients alive and progression-free at 6 months when treated with lomustine.⁷ Based on these results active chemotherapy as salvage treatment for patients with recurrent glioma is recommended, which strives to improve survival and quality of life despite inherent chemotherapy-related toxicity.

The NovoTTF-100A system (Novocure Ltd., Haifa, Israel) is a portable device delivering low intensity, intermediate frequency, alternating electric fields (Tumour Treating Fields; TTF) using non-invasive, disposable transducer arrays (Fig. 1A). These fields physically

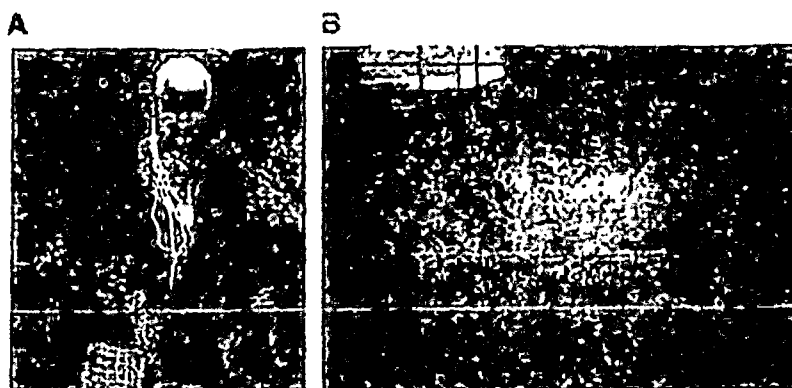


Fig. 1. Female patient wearing the portable NovoTTF-100A device (A). Grade 2 skin rash underneath transducer arrays in a different patient (B). With the patients' permission.

interfere with cell division by causing misalignment of microtubule subunits in the mitotic spindle during the metaphase to anaphase transition²⁵ and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase.^{26,27} This causes failure of cytokinetic furrow formation and resultant mitotic blebbing, leading to the disruption of chromosome segregation and eventual cell death. The exact pathways by which spindle disruption and physical aggregation of macromolecules lead to cell death are unknown. TTF has been tested in several pilot clinical studies^{26,28,29} including a small single arm study as monotherapy for recurrent glioblastoma. The results of this pilot trial were promising³⁰ and served as the basis of this phase III trial comparing NovoTTF-100A monotherapy (TTF) to best active chemotherapy according to the physician's best choice (active treatment control group). This report describes for the first time the efficacy and safety of this entirely novel treatment modality compared to widely accepted active chemotherapies for the treatment of recurrent glioblastoma patients.

2. Methods

2.1. Patient selection

Patients 18 years or older with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) were eligible following radiologically confirmed disease progression (Macdonald criteria). Patients had a Karnofsky performance status $\geq 70\%$ and adequate haematologic, renal and hepatic function (absolute neutrophil count $\geq 1000/\text{mm}^3$; haemoglobin $\geq 100 \text{ g/L}$ platelet count, $\geq 100,000/\text{mm}^3$; serum creatinine level $\leq 1.7 \text{ mg/dL}$ ($<150 \mu\text{mol/L}$); total serum bilirubin level \leq the upper limit of normal and liver-function values, <3 times the upper limit of normal). Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temozolomide). There was no limit on number or type of prior

therapies or recurrences. Patients with infra-tentorial tumour location were excluded, as were patients with implanted electronic medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt). All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centres.

2.2. Study design and treatment

Patients were randomised at a 1:1 ratio to receive either TTF monotherapy (without chemotherapy) or the best available active chemotherapy according to the local physician's choice (active control). Randomisation was performed using random block sizes and was stratified by centre and according to whether patients underwent surgery for their latest recurrence prior to trial entry. Assigned treatment had to start within 1 week of randomisation, and was to be continued until disease progression or intolerance.

For patients assigned to the TTF group four transducer arrays were placed on the patient's shaved scalp and connected to a portable, battery or power supply operated device (NovoTTF-100A) which was set to generate 200 kHz electric fields within the brain in two perpendicular directions (operated sequentially). Field intensity was set at $>0.7 \text{ V/cm}$ at the centre of the brain. Patients were trained on how to operate the device and then continued treatment at home. Treatment was continuous while maintaining normal daily activity. Transducer arrays were replaced by the patients, their caregivers or device technicians once or twice a week. Prior to placement, the scalp was shaved carefully with an electric razor in order to avoid skin wounding, transducer arrays were supplied sterile. Although uninterrupted treatment was recommended, patients were allowed to take treatment breaks of up to an hour, twice per day, for personal needs (e.g. shower). In addition, they were allowed to take 2–3 days off treatment at the end of each 4 weeks of treatment (which is the minimal

required treatment duration for TTF therapy to reverse tumour growth).³⁰

Patients assigned to the active control received chemotherapy at the local investigators discretion. The best available chemotherapy was prescribed according to local practice and depending on prior treatment exposure.

2.3. Patient surveillance and follow up

Baseline examinations included a gadolinium-enhanced magnetic resonance imaging (MRI) of the brain, full blood counts, blood chemistry tests, blood coagulation tests, electrocardiogram (ECG), physical examination including a detailed neurological examination and quality of life (QoL) questionnaire (European Organisation for Research and Treatment of Cancer (EORTC) QLQ C-30).

Patients were followed once a month, including laboratory tests. MRI was repeated every 2 months. QoL questionnaires were completed at baseline and then every 3 months. Tumour response and progression were determined by blinded central radiology review, according to Macdonald criteria.³¹ When an MRI could not be obtained, progression was assessed clinically based on neurological status, steroid dosing, adverse events and investigator assessment of progression.

Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria (NCI CTC V3.0)

2.4. Statistical analysis

The primary end-point was OS. Secondary end-points were progression free survival (PFS), the percentage of patients alive and progression-free at 6 months (PPS6), 1-year survival rate, radiological response rate (RR), QoL and safety. OS and PFS were computed from the day of randomisation until event or censored at last follow-up according to the Kaplan–Meier method, with 2-sided logrank statistics for comparison. The study had an 80 per cent power at a significance level of 0.05 to detect a 60 per cent increase in median OS (hazard ratio for death, 0.63). All analyses were performed using the intent to treat population of all randomised patients, patients lost to follow-up were censored at the time of last contact. A Cox proportional hazards model was used to adjust for confounding baseline variables (continuous and categorical). The survival data were tested for proportional hazards and the assumption of proportionality met. The Cox model was performed in two steps; first, all protocol pre-specified baseline variables were tested directly for interactions with OS; then a reduced model was performed testing the effect of all variables with significant interactions ($p < 0.05$) with OS together on the treatment effect of TTF versus active chemotherapy. Secondary end-points are presented without adjustment. QoL is pre-

sented as change from baseline to 3 months for each of the subscale domains and symptom scales of the QLQ-C30 questionnaire.

2.5. Organisational aspects

The trial was registered on www.clinicaltrials.gov, NCT#00379470. The trial was funded and sponsored by Novocure Ltd. Statistical analysis was performed by David Steinberg. The manuscript was written by Roger Stupp and Eilon Kirson, with substantial input by all co-authors. The final manuscript was reviewed and approved by all authors. The statistician and the corresponding author had unrestricted access to all data.

2.6. Role of the funding source

Representatives of the study sponsor were involved in the study design, data collection, data analysis, data interpretation and writing of the report. Data analysis was performed by David Steinberg, a compensated independent biostatistician. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Patients

From September 2006 until May 2009, 237 patients from 28 institutions in 7 countries were randomly assigned to receive TTF monotherapy (120 patients) or active control chemotherapy (117 patients). The baseline patient characteristics were balanced (Table 1). The median age was 54, and a quarter of the patients had undergone some surgical resection of the recurrent tumour prior to enrolment into the trial. More than 80% of patients had failed two or more prior lines of chemotherapy (\geq second recurrence) and 20% of the patients had failed bevacizumab prior to enrolment. Histology was per local pathological diagnosis; in 8% a history of a prior lower grade glioma had been reported (secondary glioblastoma). *Methyl-guanine methyl-transferase (MGMT)* gene promoter methylation, an important predictive factor for benefit of temozolomide chemotherapy in newly diagnosed glioblastoma, was not assessed in this trial of patients with recurrent disease.

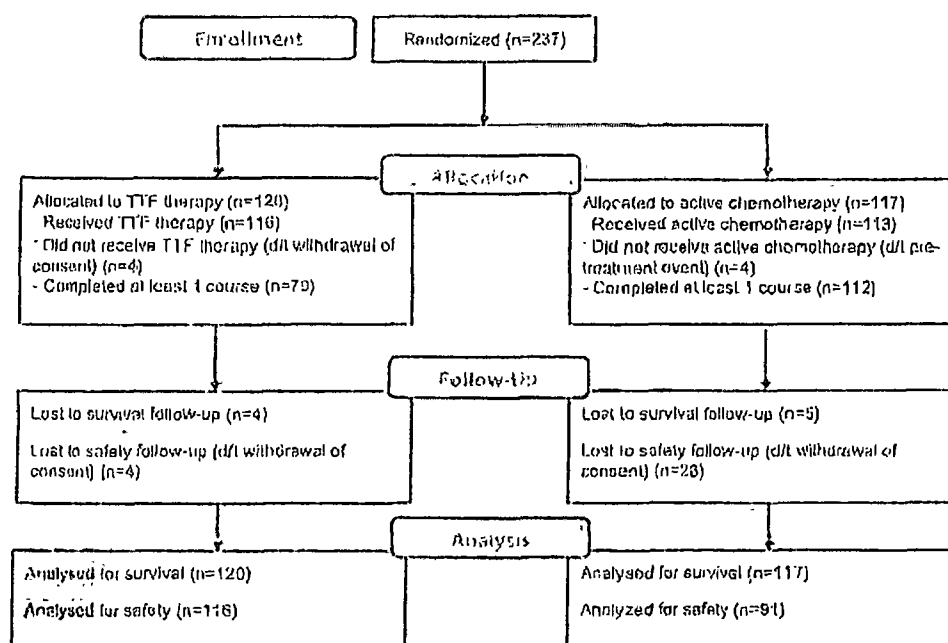
3.2. Patient disposition, treatment and compliance

In the TTF group, 116 of 120 patients (97%) started treatment and 93 patients (78%) completed 4 weeks of therapy (1 cycle). Twenty-seven patients discontinued treatment early, often within a few days, due to non-compliance or inability to handle the device (trial flow

diagram). Four patients had pre-treatment events related to the progressive nature of their disease and never started therapy with the device. In the TTF patients who started treatment (116 patients) mean compliance was measured by downloading a log file from the device, which recorded the actual time TTF therapy was delivered. Median compliance was 86 per cent (range 41–98%) of the time in each treatment month, translating into a mean use of 20.6 h per day.

apy (6.6 versus 6.0 months, respectively). One-year survival proportion was 20% in both groups, the 2- and 3-year survival rates survival rates were 8% (95% CI 4, 13) and 4% (95% CI 1, 8) versus 5% (95% CI 3, 10) and 1% (95% CI 0, 3), for TTF versus active control, respectively (Fig. 1A). The hazard ratio for death was 0.86 (95% CI 0.66, 1.12) in favour of NovoTTF ($p = 0.27$). Adjusting for baseline characteristics using a Cox proportional hazards model did not substantially

trial flow diagram



In the active control group, 113 of 117 patients (97%) started chemotherapy and all but 1 patient completed one full treatment course of the chosen chemotherapy. In four patients disease related adverse events and tumour progression prevented the initiation of the planned chemotherapy, they only received supportive care (hospice care). Twenty-one patients randomised to the control group decided not to return to the investigational site for treatment, thus details on disease progression and toxicity are not available. Most of patients received single agent or a combination chemotherapy regimen containing bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%; Supplementary Table 1).

3.3. Survival, progression and radiological response

At a median follow up of 39 months, 220 patients had died (93%). Median survival was marginally higher in the TTF group compared to active control chemother-

apy (6.6 versus 6.0 months, respectively). One-year survival proportion was 20% in both groups, the 2- and 3-year survival rates survival rates were 8% (95% CI 4, 13) and 4% (95% CI 1, 8) versus 5% (95% CI 3, 10) and 1% (95% CI 0, 3), for TTF versus active control, respectively (Fig. 1A). The hazard ratio for death was 0.86 (95% CI 0.66, 1.12) in favour of NovoTTF ($p = 0.27$). Adjusting for baseline characteristics using a Cox proportional hazards model did not substantially

alter the results. In the active chemotherapy control arm of the trial, survival was not significantly affected by the choice of chemotherapy (Cox proportional hazards test; $p = 0.66$). More objective radiological responses (partial and complete responses) were seen in the TTF group than in the active control chemotherapy group (14 versus 7, respectively), translating into a response rate in evaluated patients of 14.0% (95% CI 7.9–22.4%) versus 9.6% (95% CI 3.9–18.8%), respectively (chi squared $p = 0.19$). All three complete responses were observed in the TTF group. Two exemplary partial responses from TTF are shown in Fig. 3.

The trial had been designed for superiority. Since the control group in the trial is an active chemotherapy control which showed similar efficacy to that seen in previous trials and the device was used as monotherapy it is reasonable to analyse the results also in the context of a non-inferiority analysis. The HR for death in the TTF group compared to the active control chemotherapy group was below 1.0 (0.86; 95% CI 0.66–1.12), indi-

Table 1
Baseline characteristics.

	Tumour Treatment Fields (TTF) (n = 120) # pts (%)	Active control (n = 117) # pts (%)
Characteristics		
Age, median (range)	54 years (24–80)	54 years (29–74)
Gender		
Male	92 (77)	73 (62)
Females	28 (23)	44 (38)
Histology		
Glioblastoma	100%	100%
Prior lower grade glioma	10 (8)	9 (8)
Karnofsky performance status, median (range)	80% (50–100)	80% (50–100)
Steroid use at enrolment		
Yes	55 (46)	62 (53)
No	55 (46)	49 (42)
Unknown	10 (8)	6 (5)
Largest tumour diameter at randomisation, median (range)	6.1 cm (0–15.2)	5.5 cm (0–16.2)
Interval from initial glioma diagnosis, median (range)	11.8 months (3.2–99.3)	11.4 months (2.9–77.1)
Prior therapy		
1st recurrence	11 (9)	17 (15)
2nd recurrence	58 (48)	54 (46)
3rd or greater recurrence	51 (43)	46 (39)
Surgery		
Debulking before enrolment	33 (28)	29 (25)
Debulking at any stage	95 (79)	99 (85)
Biopsy only	25 (21)	18 (15)
Radiotherapy		
100%	100%	100%
With concomitant temozolomide	103 (86)	96 (82)
No concomitant temozolomide	15 (13)	20 (17)
Unknown	2 (1)	1 (1)
Prior adjuvant (maintenance) temozolomide		
Median no of cycles	4 (0–19)	3 (0–27)
Prior bevacizumab		
	23 (19)	21 (18)

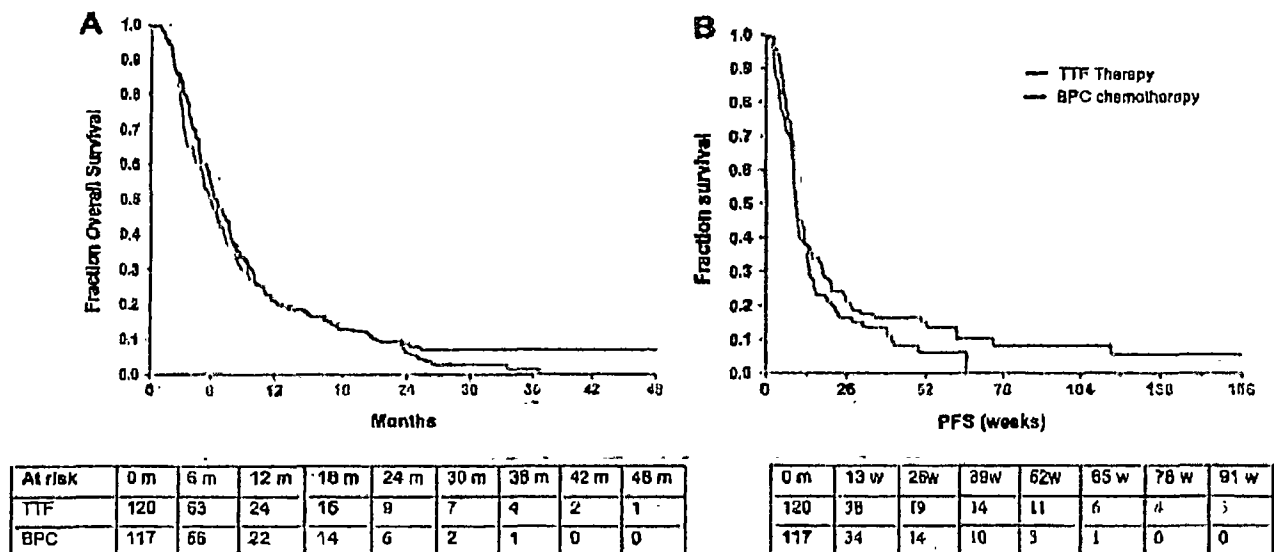


Fig. 2. Overall survival (A) and progression free survival (B) Kaplan-Meier curves.

cating that TTF may be at least equivalent to active chemotherapy.

PFS showed a similar trend in favour of TTF patients as seen for OS (Fig. 1B). Median PFS was 2.2 and

2.1 months for TTF and active control groups, respectively (Fig. 2; HR 0.81, 95% CI 0.60–1.09; log rank $p = 0.16$). PF86 was 21.4 per cent (95% CI 13.5–29.3) in the TTF group and 15.1 per cent (95% CI 7.8–22.3) in the active control group (chi squared $p = 0.13$).

3.4. Safety and toxicity

As expected from the mechanism of action of TTF therapy and the fact that its delivery is localised to the head, the typical systemic side-effects of chemotherapies were not observed in the TTF treated patients. Mild to moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16% of TTF patients (Fig. 1B). This condition was easily treated with topical corticosteroids, resolved completely after treatment, was stopped and did not require substantial treatment breaks.

Patients receiving active control chemotherapy experienced toxicity related to pharmacologic mechanism of the agents used. A list of grade 2–4 adverse events by organ system and adverse event terms seen in more than 2% of patients in either group is presented in Table 2. As expected, there were significantly more gastrointestinal, haematological and infectious adverse events seen in the chemotherapy group than in the TTF group. Severe

(grades 3 and 4) toxicity was observed in only 3% of patients.

3.5. Quality of life

Longitudinal Quality of Life (QOL) could be analysed in the patients who remained on study therapy for ≥ 3 months and for whom QoL data were available (63 patients, 27%). In the domains of global health and social functioning no meaningful differences between chemotherapy and TTF were observed. However, cognitive and emotional functioning favoured TTF. Physical functioning may be slightly worse with TTF, while role functioning favoured TTF (Fig. 4A). Symptom scale analysis is in accordance to treatment-associated toxicity; appetite loss, diarrhoea, constipation, nausea and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF treatment group (Fig. 4B).

3.6. Treatment after progression

In order to rule out the effect of subsequent treatments on the OS results reported above, we compared the number and type of post-progression treatments patients received after failing the trial therapy. Due to

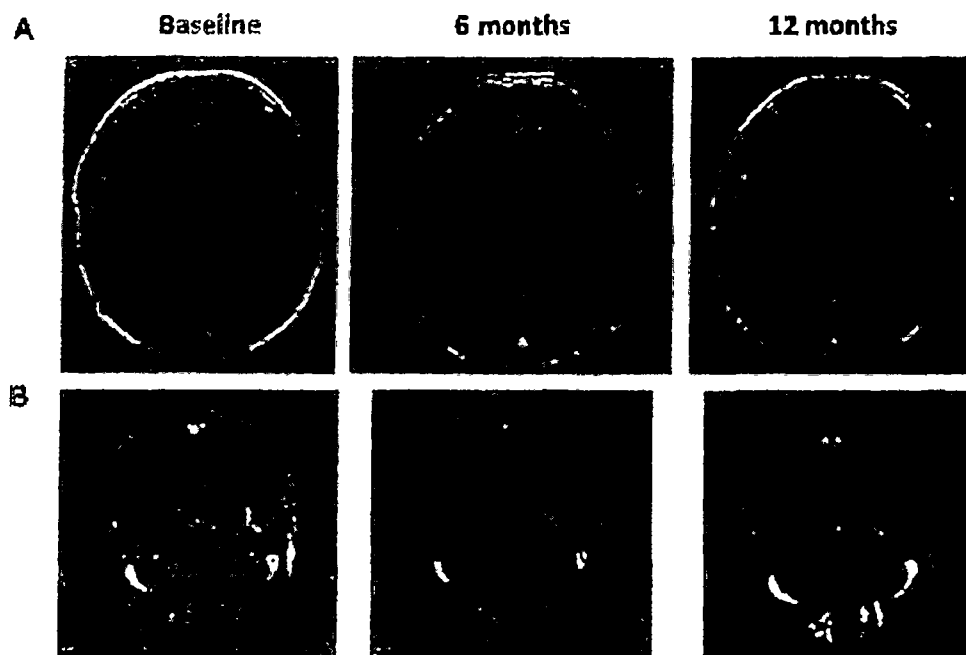


Fig. 3. Exemplary T1 weighted magnetic resonance imaging (MRI) images with gadolinium from two Tumour Treatment Fields (TTF) patients with partial response to therapy. (A) A 48 years old male with prior grade II astrocytoma which transformed to glioblastoma (based on tissue biopsy). The subject progressed 7 months after receiving chemoradiotherapy, and subsequently responded to TTF therapy (partial response at 12 months) and remained stable for an additional 36+ months on TTF. (B) A 55 years old male with primary glioblastoma who recurred for the third time after receiving chemoradiotherapy, adjuvant temozolomide (2 cycles), bevacizumab with irinotecan (3 months) and erlotinib with sorafenib (one cycle). The subject had a partial response to TTF therapy after 4 months of treatment and remained stable for an additional 8 months while on TTF.

Table 2

Treatment-emergent adverse events \geq grade 2 by body system.

System	Adverse event term	Tumour Treatment Fields (TTF) (n = 116) % (% gr. 3 + 4)	Active control (n = 91) % (% gr. 3 + 4)
Haematological		3 (0)	17 (4)
	Leucopenia	0 (0)	5 (1)
	Neutropenia	0 (0)	2 (1)
	Thrombocytopenia	1 (1) ^a	7 (2)
Gastrointestinal disorders		4 (1)	17 (3)
	Abdominal pain	0 (0)	3 (0)
	Diarrhoea	0 (0)	6 (2)
	Nausea/vomiting	2 (0)	7 (0)
General deterioration and malaise		5 (1)	6 (1)
Infections		4 (0)	8 (1)
Skin rash (transducer arrays)		2 (0)	0 (0)
Metabolic and nutrition disorders		4 (1)	6 (3)
Musculoskeletal disorders		2 (0)	5 (0)
Nervous system disorders		30 (7)	28 (7)
	Brain oedema	0 (0)	2 (0)
	Cognitive disorder	2 (1)	2 (1)
	Convulsion	7 (2)	5 (2)
	Dysphasia	2 (0)	1 (0)
	Headache	8 (1)	6 (0)
	Hemianopsia	1 (0)	3 (1)
	Hemiparesis	3 (1)	2 (1)
	Neuropathy peripheral	2 (0)	2 (0)
Psychiatric disorders		5 (0)	4 (0)
Renal and urinary disorders		3 (1)	3 (0)
Respiratory disorders		1 (0)	3 (1)
Vascular disorders		3 (1)	4 (3)
	Pulmonary embolism	1 (1)	2 (2)
	Hypertension	1 (0)	1 (1)
	Deep vein thrombosis	1 (0)	1 (0)

^a Thrombocytopenia from prior chemotherapy, normalised subsequently.

the very advanced stage they were recruited to the study (most patients were at their second or subsequent recurrence), only 5.8% of the TTF-treated patients and 10.3% of the chemotherapy-treated patients received subsequent salvage antitumour therapy (chi square $p = 0.24$) (mainly bevacizumab, irinotecan, nitrosoureas and temozolomide). The majority of patients received only supportive care once tumour progression developed.

4. Discussion

Tumour treatment with alternating electrical fields that interfere with the metaphase to anaphase transition in dividing tumour cells is an entirely novel cancer treatment modality. We report the first prospective, randomised, controlled study using this new treatment modality in the most aggressive primary brain tumour. Although glioblastoma diffusely infiltrates the brain, it almost never metastasises and is thus amenable to a loco-regional therapy.

Prognosis of patients with recurrent glioblastoma is poor, and chemotherapy is usually recommended. Depending on prior treatments and treatment centre expertise, variable chemotherapy agents alone or in combination are commonly prescribed. Our randomised trial compared this standard chemotherapy per local

practice (active treatment control group) with TTF in a prospective, multicentre phase III trial. Although the trial did not reach its primary end-point of improved survival compared to active chemotherapy, this new minimally invasive and chemotherapy-free local treatment modality demonstrated a statistically non-significant increased response rate (14 versus 9.6%, $p = 0.19$), an improved PFS6 rate (21% versus 15%, $p = 0.13$), and a trend towards reduction of the risk of death (hazard ratio 0.86, 95% CI 0.66–1.12, $p = 0.27$), as well as sustained improvement in QoL.

These results cannot be explained by subsequent salvage chemotherapy, as few patients received additional therapy after failure of protocol treatment. Importantly, the majority of our patients were recruited to the trial at an advanced stage of the disease, after failure of two or more chemotherapy agents, while other trials in recurrent glioblastoma usually only enrol patients at first recurrence. It is also notable that 20% of patients had failed prior bevacizumab therapy, a population that usually fares poorly with most subsequent treatments.

One limitation of the study was the absence of a placebo or treatment-free control arm. In the setting of advanced disease and chemotherapy considered indicated and effective, such a control would hardly have been acceptable to patients and physicians alike. Fur-

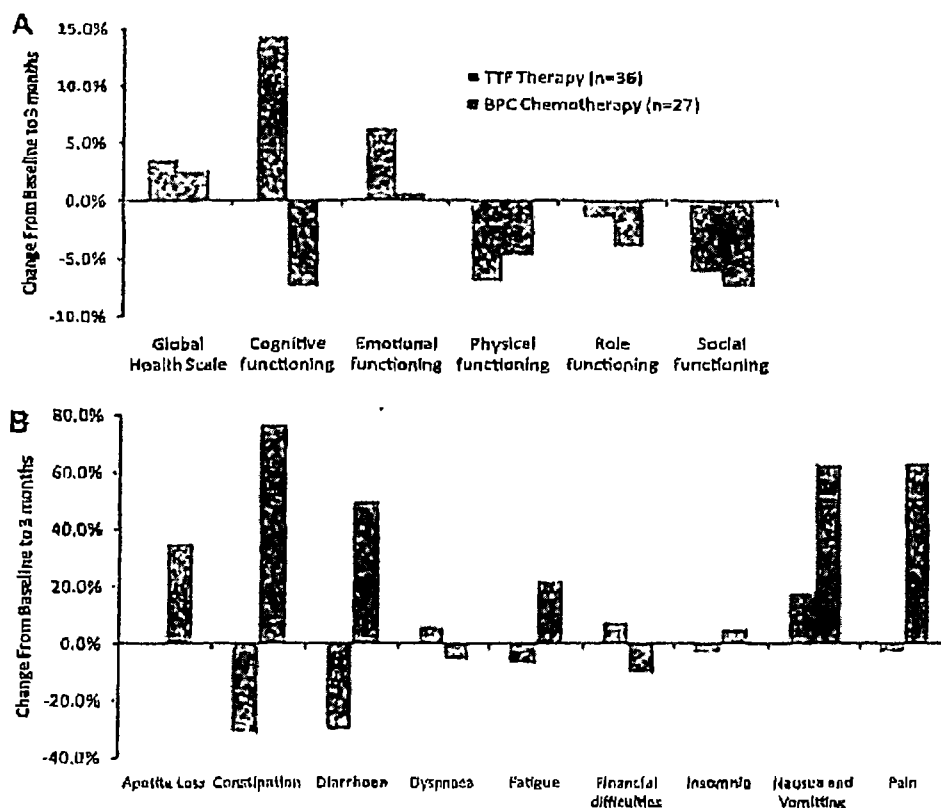


Fig. 4. QLQ C30 longitudinal change from base to 3 months. (A) General functional scales (an increase in percentage corresponds to an increase in QoL). (B) Symptom scales (an increase in percentage corresponds to a decrease in QoL).

thermore, chemotherapy with lomustine has shown superior efficacy versus investigational treatments in two recent randomised trials. And based on high response rates and prolonged survival compared to historical controls bevacizumab has received accelerated Food and Drug Administration (FDA) approval. Furthermore, the observation of objective responses in 14 patients with NovoTTF alone (median time since end of prior RT 7 months, thus unlikely to be all pseudoprogression) strongly suggests singular activity of this device.

Another limitation is the somewhat heterogeneous patient population, with patients included after progression of one or several lines of prior chemotherapy. This underscores the demand from patients for further treatments, even when the expected benefit of a 2 months prolongation in PFS may appear modest. In the ongoing randomised phase III trial for newly diagnosed glioblastoma, only patients non-progressive after completion of chemoradiation are eligible (Novocure EF-14, www.clinicaltrials.gov, NCT#00916409).

As expected with a local treatment, toxicity was limited to skin irritation from transducer arrays (Fig. 1B). After proper instructions, most patients became independent in handling this device and replacing transducer arrays, allowing them to be ambulatory and even going to work. Despite the inconvenience of carrying and

using the device almost permanently, compliance was high and patients reported improvement in QoL in the absence of chemotherapy related toxicities.

In vitro and animal experiments suggest enhanced effect when TTF is combined with chemotherapy.^{28,32} We therefore initiated a subsequent randomised phase III trial currently enrolling newly diagnosed glioblastoma patients after completion of standard radiochemotherapy, parallel to starting the adjuvant or maintenance temozolomide chemotherapy. Patients randomised to the experimental arm will receive TTF in addition to maintenance temozolomide (www.clinicaltrials.gov, NCT#00916409).

Based on the result of this trial TTF therapy has recently been approved in the US and Europe for the treatment of recurrent glioblastoma (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251669.htm).

The universal anti-cancer effect of TTF may be applicable to other solid tumour types, alone or in combination with chemotherapy. In particular, in a situation of morbidity induced by a heavy local tumour burden, and in conditions where further radiotherapy is not an option, this non-invasive treatment may allow for a clinical benefit and will substantially expand our treatment armamentarium.

Conflict of interest statement

Eilon Kirson and Uri Weinberg are employees of Novocure Ltd., and have stock options in the company.

Herwig Kostron has received honoraria from Novocure Ltd.

Yoram Palti is the inventor of the Novo-TTF principle. He received consulting honoraria and travel support by Novocure Ltd.

Nina Paleologos has served on advisory boards and speakers bureau to Genentech, Merck & Co (previously Schering-Plough).

Susan Panullo has received research grants from Novocure, NTI Pharma, Eisai, Immunocellular and Parexel, and honoraria for lectures from Merck & Co (previously Schering-Plough).

Zvi Ram is a board member for Novocure, and received consultancy honoraria.

Jeffrey Raizer has received research support from Novocure Ltd., performed consultancy for Merck and Genentech/Roche, and lectures on behalf of Merck & Co, Genentech and Enzon.

David Schiff has performed consultancy for Genentech and Tau Pharmaceuticals.

Andrew Sloan has provided consultancy to Genentech/Roche, Real Bio Inc., Nautifiber Solutions, Surgical Theatre and Montoris Medical Inc.

Roger Stupp has served on scientific advisory boards for Merck-Serono, Roche, Actelion, MDxHealth (previously OncoMethylomeSciences) and Merck and Co (previously Schering-Plough).

Manfred Westphal has received consultancy honoraria from Roche, OncoScience and Ark Therapeutics.

Eric T. Wong has received research support from Novocure Ltd.

The following authors declare no potential conflict of interest: Jeffrey Bruce, Lawrence Chin, Rees Cosgrove, Vladimir Dbaly, Herbert Engelhard, Philip Gutin, Volkmar Heidecke, Silvia Hofer, Andrew Kanner, Lara Kunscher, Joseph Landolfi, Frank Licheberman, Marc Malkin, Maximilian Mehdorn, Franz Paya, Martin Sorek, David Steinberg, J. Lee Villano, and Robert Weil.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejca.2012.04.011>.

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NovoTTF-100A: a new treatment modality for recurrent glioblastoma

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NovoTTF-100A (Novocure Inc., Haifa, Israel) is a first-of-a-kind device approved by the US FDA for the treatment of recurrent glioblastoma. It works by emitting a low-intensity, intermediate-frequency (200 kHz), alternating electric field administered via insulated transducer arrays applied onto the scalp. The electric field penetrates the brain and inhibits the growth and proliferation of glioblastoma by interfering with tumor cell mitosis at anaphase. Results from a Phase III clinical trial indicate that the efficacy of NovoTTF-100A is equivalent to standard-of-care chemotherapy. The side effect profile favors device-treated patients, obviating typical toxicities associated with chemotherapy or targeted drugs, and results in improvements in their quality of life. NovoTTF-100A is a new modality of cancer treatment that offers equivalent efficacy, but less toxicity, to recurrent glioblastoma patients when compared with existing treatments.

Keywords: chemotherapy • electric field • glioblastoma • NovoTTF-100A • tumor-treating field

Overview of the market

Despite continuing research in drug treatments for glioblastomas, median patient survival remains a dismal 14.6 months from the time of initial diagnosis using combined radiation and chemotherapy [1]. Fewer than 10% of patients survive to the 5-year time point [2]. At the time of glioblastoma recurrence or progression, the overall survival (OS) of patients is even worse – typically 6 months or less [3]. The only US FDA-approved medical treatment for recurrence is bevacizumab, but this drug has never been tested in a Phase III clinical trial. Current salvage treatment with bevacizumab prolongs only the progression-free survival (PFS), but not OS, and the tumor invariably progresses in an infiltrative pattern, causing neurological deficits and eventual death [4,5]. Both bevacizumab and cytotoxic chemotherapies have serious side effects that include hemorrhage, thromboembolism, infection, hypertensive crisis, renal failure, diarrhea, nausea and vomiting [4–6]. Therefore, there is a great unmet need for novel therapies that have new mechanisms of action against glioblastoma and a more favorable toxicity profile.

Introduction

NovoTTF-100A (Novocure Inc., Haifa, Israel) is a novel class of therapeutic device being used

for the treatment of recurrent glioblastoma. It works by emitting low-intensity, intermediate-frequency (200 kHz), alternating electric fields administered by insulated transducer arrays to inhibit the growth and proliferation of intracranial glioblastomas [7]. This device, which consists of the transducer arrays, electric field generator (set at a frequency of 200 kHz) and battery (Figure 1), was approved for use by the FDA on 8 April 2011 [10]. This review summarizes its mechanisms of action, Phase III efficacy and safety data, and current use in clinical practice.

Mechanism of action

NovoTTF-100A exerts its anti-tumor effect on glioblastoma cells by interfering with mitosis at anaphase. In synchronized cell culture, such a tumor-treating electric field (TTField) first disrupted cytokinesis and then impaired chromosome separation from the metaphase plates [8]. Biochemical assays also confirmed that these cells had already transited from metaphase to anaphase [8]. Immunofluorescence of treated cells demonstrated lagging chromosomes, dispersion of chromosomes, chromosome decondensation in the absence of cytokinesis, and asymmetric chromosome segregation [8,9]. Exposed cells showed no p53 induction, suggesting that cell death was mediated via a p53-independent

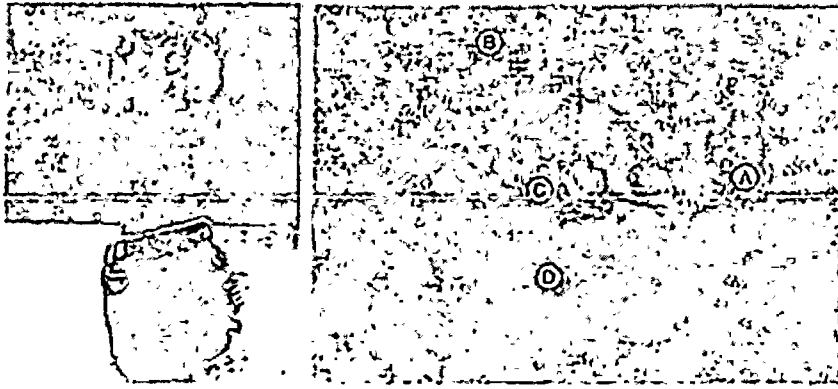


Figure 1. The NovoTTF-100A device setup. Left panel: The NovoTTF-100A device. Right panel: Two opposing pairs of transducer arrays (A) are applied to the scalp and the cables are linked to the connection box (B). The connection box is then attached to the electric field generator (C), which is connected to a power supply (D). The entire set up weighs approximately 7 lbs.

mechanism [8]. Furthermore, susceptibility to TTField is cell type dependent. Both glioma cells from rats (R-98) and humans (UB7 and U118) have a significantly decreased growth rate when exposed to TTField [9]. The best result appears to occur at an intensity of 2.25 V/cm and a frequency of 200 kHz [9]. Taken together, TTField represents a new modality of anticancer treatment via a mechanism that differs from conventional radiotherapy, cytotoxic chemotherapies or targeted kinase inhibitors. However, additional research is needed to determine the effect on postmitotic neurons and glia, as well as dividing progenitor cells, within the brain.

Clinical efficacy

NovoTTF-100A underwent initial testing in a pilot trial of ten patients with recurrent glioblastoma [7]. The results showed that the median time to disease progression was 26.1 weeks (range: 3.0–124.0 weeks), the PFS at 6 months (PFS6) was 50% (95% CI: 23–77%), and the median OS was 62.2 weeks (range: 20.3–124.0 weeks) [1]. There were two durable responses, including two patients with complete and partial responses lasting 43.3+ weeks and 30.3+ weeks, respectively [7]. These preliminary data compared favorably to benchmark outcomes from conventional cytotoxic chemotherapies, which had a response rate of 9%, PFS6 of 15%, median PFS of 9.0 weeks, and a median OS of 25.0 weeks (95% CI: 21–28 weeks) [9].

NovoTTF-100A was subsequently compared to best standard of care (BSC) chemotherapy for recurrent glioblastoma after initial temozolomide chemoradiation in a prospective, randomized, open-label Phase III clinical trial. Among the 28 centers in the USA and Europe, 237 individuals were randomized to NovoTTF-100A alone (120 subjects) or BSC (117 subjects) [10,11]. The primary end point was OS and secondary end points included PFS, PFS6, 1-year survival rate, objective radiological response, quality of life and safety. All analyses were performed on the intent-to-treat population, and Kaplan–Meier OS and PFS were computed from the time of randomization until event or censoring at last

follow-up. The trial was powered at 80%, with a significance of $p \leq 0.05$ and a hazard ratio (HR) for death of ≤ 0.67 . The median age, Karnofsky Performance Score and other clinical characteristics were balanced between the two cohorts, with the exception of slightly larger tumor size in the NovoTTF-100A group versus the BSC group, at a median size of 6.1 cm (range: 0.0–15.2 cm) and 5.5 cm (range: 0.0–16.2 cm), respectively (TABLE 1) [10,11]. BSC chemotherapies chosen by the treating physician included single-agent or combination irinotecan (31%), bevacizumab (31%), BCNU/CCNU (25%), carboplatin (13%), temozolomide (11%), combination procarbazine, CCNU and vincristine (9%), etoposide (3%), imatinib (2%), hydroxyurea (1%), or nothing (3%) [10,11]. In the intent-

to-treat population, the median OS was 28.6 versus 26.0 weeks (HR: 0.86; 95% CI: 0.66–1.12), the median PFS was 9.5 versus 9.1 weeks (HR: 0.84, 95% CI: 0.64–1.13), and the median PFS6 was 21 versus 15% for NovoTTF-100A and BSC chemotherapy, respectively (FIGURE 2) [10,11]. The data indicate that NovoTTF-100A has an equivalent efficacy when compared to salvage cytotoxic chemotherapies and targeted drugs for recurrent glioblastoma. Interestingly, patients who failed bevacizumab and then enrolled to receive NovoTTF-100A ($n = 23$) had a significantly longer survival than those who received BSC chemotherapy ($n = 21$), at 19.1 versus 13.4 weeks ($p < 0.02$), respectively [12].

Safety & tolerability

The side effect profile favors NovoTTF-100A treatment significantly more than BSC. Notably, there were only 3 versus 17% hematological toxicities, 4 versus 17% gastrointestinal side effects, and 4 versus 8% infections at grade 3 or 4 severity in the NovoTTF-100A versus BSC cohorts, respectively [10,11]. Other systemic toxicities were well-balanced between the two groups. However, scalp irritation from transducer array placement did occur at a higher frequency, with 17% grade 1 and 2 skin rash in the NovoTTF-100A subjects when compared with 0% in those treated with BSC chemotherapy [10,11]. However, none of the device-treated patients experienced skin toxicity higher than grade 2. Additional self-reported quality-of-life analysis by EORTC QLQ C-30 showed positive scores from NovoTTF-100A usage due to improved cognitive function, decreased constipation and diarrhea complications, as well as absence of pain [11,12].

Use in practice

Certain medical conditions are contraindicated in NovoTTF-100A usage and may pose unknown risks to patients. First, it is inadvisable to prescribe this device to patients with active implanted medical devices, such as cardiac pacemakers, defibrillators, deep-brain stimulators, vagus nerve stimulators and

Table 1. Baseline characteristics of subjects enrolled in the Phase III NovoTTF-100A trial for recurrent glioblastoma.

	54 (24–80) years	54 (29–74) years
Age, median (range)		
Gender:		
– Male	92 (77%)	73 (62%)
– Female	28 (23%)	44 (38%)
Histology:		
– Primary glioblastoma	110 (92%)	103 (92%)
– Secondary glioblastoma	10 (8%)	9 (8%)
Karnofsky performance status, median (range)	80 (50–100)	80 (50–100)
Corticosteroid use at the time of enrollment:		
– Yes	55 (46%)	62 (53%)
– No	55 (46%)	49 (42%)
– Unknown	10 (8%)	6 (5%)
Maximum tumor diameter at randomization, median (range)	6.1 (0.0–15.2) cm	5.5 (0.0–16.2) cm
Time from initial gliomas diagnosis, median (range)	11.8 (3.2–99.3) months	11.4 (2.9–77.1) months
First recurrence	11 (9%)	17 (15%)
Second recurrence	58 (48%)	54 (46%)
Third or greater recurrence	51 (43%)	46 (39%)
Surgery:		
– Debulking surgery prior to enrollment	33 (28%)	29 (25%)
– Debulking at any stage	95 (79%)	99 (85%)
– Biopsy only	25 (21%)	18 (15%)
Radiotherapy:	120 (100%)	117 (100%)
– Radiotherapy with concomitant temozolomide	103 (85%)	96 (82%)
– Radiotherapy without concomitant temozolomide	15 (13%)	20 (17%)
– Unknown	2 (1%)	1 (1%)
Prior adjuvant (maintenance) temozolomide	100 (83%)	89 (76%)
Median number of cycles	4 (0–19)	3 (0–27)
Prior bevacizumab use	23 (19%)	21 (18%)

Data taken from [11].

programmable ventriculoperitoneal shunts. These devices may cause reciprocal electromagnetic interference, induction or both, and the extent of this risk is unknown. Second, patients with major skull defects cannot receive this treatment. For example, those with a missing section of the calvarium may experience elevated electric field strength on the brain. However, those with healed burr holes and craniotomy sutures can receive this treatment without complications. Third, metals within the brain are also contraindicated because NovoTTF-100A has not been tested in patients with bullet fragments or aneurysm clips in their head. Last, those with hypersensitivity to hydrogel, which is used as a

conductive interface between the transducer array disks and the scalp, may not be able to receive this treatment.

Pretreatment evaluation consists of baseline history, physical examination (including evaluation of skin integrity on the scalp), blood work and gadolinium-enhanced head MRI. The MRI images are used to construct a mapping diagram for placement of the transducer arrays. Typically, there are two pairs of opposing arrays, which are separately color coded (figure 1). The wires of the arrays are then connected to the electric field generator and power supply (figure 1). The patient's hair is then shaved off with an electric shaver instead of a razor in order to avoid superficial

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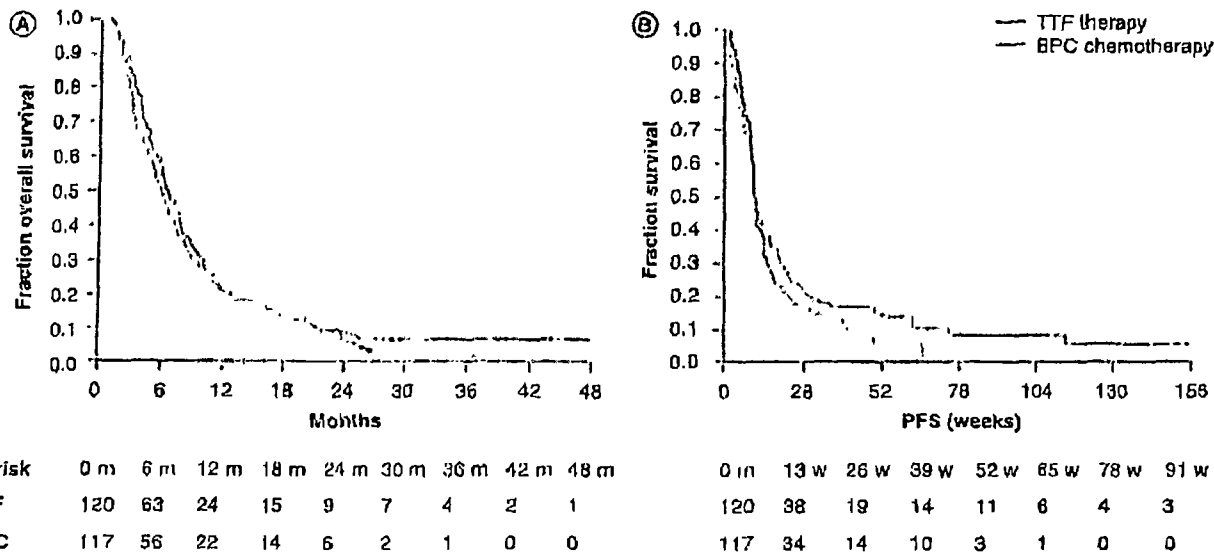


Figure 2. Data from a Phase III NovoTTF-100A trial for recurrent glioblastoma. (A) Kaplan-Meier curves showing equivalent overall survival between the NovoTTF-100A therapy group and the BPC active control. (B) Kaplan-Meier progression-free survival curves showing a greater number of subjects with disease stabilization in the NovoTTF-100A-treated group than BPC active control: four subjects without disease progression at 78 weeks and three at 91 weeks versus none in the control. BPC: Best physician choice; m: Months; PFS: Progression-free survival; w: Weeks. Reproduced with permission from [11].

cuts. The scalp is then cleaned with alcohol prior to application of the arrays. This procedure typically requires the help of another individual and it is necessary to bring a family member or assistant to learn array placement and operation of the NovoTTF-100A device. Follow-up clinic visits are scheduled monthly in the first 3 months and then every 2 months thereafter. Gadolinium-enhanced head MRI is performed once every 2 months for monitoring the status of glioblastoma during treatment.

The efficacy of NovoTTF-100A on brain tumors other than glioblastoma is unknown. However, other gliomas may respond to the same frequency (200 kHz) emitted by the NovoTTF-100A device, based on published preclinical data. However, it is still unknown whether or not TTF field at 200 kHz would be effective in controlling metastatic brain tumors because the optimal frequency for specific metastasis may be different. For example, in preclinical cell culture melanoma was most sensitive at a frequency of 120 kHz [9].

Regulatory affairs

NovoTTF-100A is currently approved by the FDA and the EMA for the treatment of recurrent or progressive glioblastomas.

Conclusion

NovoTTF-100A is a novel therapy for the treatment of recurrent glioblastoma. It emits TTF field that interferes with dividing tumor cells at anaphase. The clinical trial results indicate that it has comparable efficacy, and less toxicity, when compared to conventional drug treatments in the recurrence setting.

Expert commentary

The Phase III clinical trial demonstrated comparable, but not superior, efficacy when compared to conventional drug treatments. This result is likely to be influenced by a number of factors. First, the population of patients with recurrent glioblastomas has neurological deterioration and death within a shorter time than those with newly diagnosed disease. As a result, these patients may deteriorate early and therefore their tumors may not receive enough exposure to NovoTTF-100A treatment. Unlike conventional cytotoxic chemotherapies that have a biological effect lasting the entire duration of the treatment cycle (typically 4–6 weeks), the TTF field needs to be applied continuously otherwise the anti-tumor effect would disappear as soon as the generator is switched off. Consistent with this reasoning, the per-protocol analysis of the Phase III trial data, in which patients who received less than 4 weeks of NovoTTF-100A treatment were removed from analysis, showed that NovoTTF-100A offered a statistically significant survival advantage when compared to BSC chemotherapy. Second, compared to newly diagnosed glioblastomas, recurrent glioblastomas have additional genetic alterations making them more resistant to treatment [13,14]. Therefore, NovoTTF-100A may have a greater benefit to newly diagnosed patients than those with recurrent disease. A Phase III clinical trial is currently underway investigating the efficacy of NovoTTF-100A with temozolomide chemoradiation compared to standard temozolomide chemoradiation for newly diagnosed glioblastoma. Last, NovoTTF-100A does not appear to have overlapping toxicity with conventional drug treatments [10,11]. Therefore,

combining it with cytotoxic chemotherapies or targeted agents can potentially result in increased efficacy and without added toxicity. The pivotal Phase III trial did include patients after failure of polifeprosan 20 with carmustine implant (Gliadel wafer) [1]. However, for patients who have undergone wafer implantation, it would be best to withhold the use of NovoTTF-100A until complete dissolution of the wafer, which typically occurs in 4 weeks. However, more preclinical data are needed in order to find the optimal NovoTTF-100A and drug combinations before they can be applied in a clinical trial setting.

Five-year view

In the next 5 years, more preclinical studies are needed in order to determine the mechanisms of TTFeld's action on tumor cells. The results would most likely offer ideas for investigator-initiated clinical research that would help to maximize the efficacy of NovoTTF-100A against glioblastomas. This will most likely

be accomplished by the addition of drugs that have synergistic or additive activities. A logical combinatorial treatment would include NovoTTF-100A and bevacizumab because these two therapies do not have overlapping toxicity and both are approved by the FDA for the treatment of recurrent glioblastomas. Furthermore, the device could also be used to treat patients with metastatic brain tumors. However, more preclinical and clinical research is needed to support its use in these patients, as well as the specific type of metastatic brain tumor that shows sensitivity to TTFeld.

Financial & competing interests disclosure

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Key issues

- NovoTTF-100A (Novocure Inc., Haifa, Israel) emits a low-intensity, intermediate-frequency (200 kHz) alternating electric field that treats recurrent glioblastomas.
- NovoTTF-100A exerts its anti-tumor effect on glioblastoma cells by interfering with mitosis at anaphase.
- NovoTTF-100A treatment offers comparable efficacy when compared to conventional drug treatments, including bevacizumab, for recurrent glioblastoma.
- The toxicity profile favors NovoTTF-100A over conventional drug treatments.

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By Philip H. Gutin, MD, and Eric T. Wong, MD

Overview: Tumor treating fields (TTF) therapy is a novel antimitotic, electric field-based treatment for cancer. This nonchemical, nonablative treatment is unlike any of the established cancer treatment modalities, such as surgery, radiation, and chemotherapy. Recently, it has entered clinical use after a decade of intensive translational research. TTF therapy is delivered to patients by a portable, battery-operated, medical device using noninvasive transducer arrays placed on the skin surface surrounding the treated tumor. TTF therapy is

now a U.S. Food and Drug Administration (FDA)-approved treatment for patients with recurrent glioblastoma (GBM) who have exhausted surgical and radiation treatments. This article will introduce the basic science behind TTF therapy, its mechanism of action, the preclinical findings that led to its clinical testing, and the clinical safety and efficacy data available to date, as well as offer future research directions on this novel treatment modality for cancer.

THE DEFINITION of the electric field is attributed to Michael Faraday in the 1820s and was later formulated by James Clerk Maxwell in his electromagnetic theory in 1865.¹ It is a field of electric forces that surround a source charge. When a test charge is placed within an electric field, a force acts on it. Negative charges attract positive charges, while similar signed charges repel each other. As seen in Fig. 1A, an electric field surrounding a source charge can be described using diverging lines of force. The closer the test charge is to the source charge, the closer the lines of force are to each other, which represents higher field intensity.

To understand the effects of electric fields within cells, it is important to introduce three definitions. First, electric fields can be uniform or nonuniform. A uniform electric field is represented by parallel lines of force (Fig. 1B). A nonuniform electric field is represented by converging or diverging lines of force (Fig. 1A and 1D). Second, an electric field can be a constant field or a time-varying field, resulting in electrostatic or electrodynamic phenomena, respectively. In a constant field, the source charges remain the same over time. A test charge will move in one direction within a constant electric field toward the oppositely charged source (Fig. 1B). In a time-varying or alternating electric field, the charge of the sources alternates over time (Fig. 1C). Third, the test charge can be an electric charge or an electric dipole (an element with a positive charge on one end and a negative charge on the opposite end). An electric charge will move back and forth, while a dipole will rotate within an alternating uniform electric field and align with the direction of the field. In a nonuniform converging electric field, both dipoles and charges move in the direction of the higher field intensity through a process known as dielectrophoresis (Fig. 1D).

Mechanism of Action of TTF Therapy

Over 100 years after Maxwell's original publication, Yoram Palti, MD, PhD, hypothesized that properly tuned alternating electric fields at physiological intensities (i.e., 1–3 V/cm) would disrupt the mitotic process of dividing cancer cells.^{2,3} Dr. Palti hypothesized and subsequently demonstrated in vitro that at frequencies between 100 and 300 kHz, alternating electric fields disrupt the formation of the mitotic spindle during metaphase and lead to dielectrophoretic movement of charged and/or polar molecules and organelles during anaphase and telophase, disrupting normal cytokinesis and leading to apoptosis.^{2,3} According to this model, the first mechanism of action is explained by the fact

that the tubulin subunits are one of the most polar molecules in the cell. These tubulin subunits align in the direction of the applied electric field (Fig. 2A), interfering with the normal polymerization of the mitotic spindle, which results in formation of abnormal mitotic figures in vitro.³ The second mechanism of action is explained by examining the change in shape of the electric field within a dividing cell from anaphase to telophase. When the cell division axis is aligned with the direction of the electric field, the field lines that enter the cell at one end converge at the cytokinetic furrow between the developing daughter cells and then diverge on the opposite side (Fig. 2B). This nonuniform electric field within the cell generates dielectrophoretic forces that act on polar and charged elements in the cell, pushing them toward the cytokinetic furrow leading to violent blebbing of the plasma membrane.³ This finding was also validated by researchers from Beth Israel Deaconess Medical Center and may be mediated by improper placement of the contractile elements that form the cytokinetic ring on anaphase entry.⁴

Preclinical Studies of the Antitumor Effects of TTF Therapy

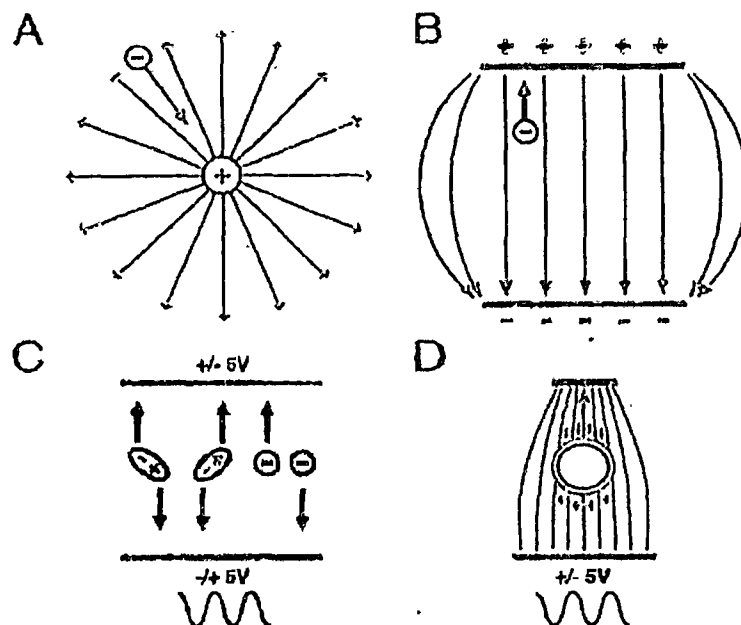
Between 2004 and 2010, a series of publications and conference presentations addressed the issue of the applicability range of TTF therapy to different in vitro and in vivo cancer models either alone or in combination with standard chemotherapy.^{5,6-8} Tables 1 and 2 summarize the state-of-the-art preclinical research with TTF therapy. TTF therapy has been shown to effectively inhibit cancer cell growth in various cell lines in vitro (Table 1). This effect was clearly dose (field intensity) dependent in the range of 1 to 3 V/cm.⁵ The optimal frequency for the inhibitory effect of TTF therapy differed between cell types and was inversely related to cell size (Table 1; e.g., glioma cell cultures at 200 kHz^{3,5}). In addition, based on the directional nature of TTF

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Fig. 1. Electric field theory. (A) Opposite charges attract. (B) A constant, uniform, electric field. (C) Charges and dipoles in a time-varying, uniform electric field. (D) A dipole in a time-varying, nonuniform electric field (dielectrophoresis).



therapy, its antimitotic effect in cultures was enhanced by sequentially applying more than one field direction to the treated cells.⁶ The combination of TTF therapy with different chemotherapeutic agents has been shown to have at least additive if not synergistic effects.^{7,8} Specifically, the combination of TTF therapy with temozolomide in glioma cell lines was shown to be additive. Interestingly, in breast cancer cells, TTF therapy showed overt synergism with taxanes (e.g., paclitaxel), probably a result of the temporal

proximity of taxanes' effect in metaphase and TTF therapy's mitotic interference on cell entry into anaphase.⁹

TTF therapy has been tested in numerous *in vivo* cancer models (Table 2).^{3,5,8,10} Noninvasive application of TTF therapy to animals was performed using electrically insulated transducer arrays placed on the head or torso surrounding the region of the tumor. Inhibition of tumor growth was seen in each of these models when the correct frequency of TTF therapy was applied. Specifically, 200 kHz TTF therapy applied in two sequential and perpendicular field directions lead to significant ($p < 0.01$) inhibition of a syngeneic, orthotopic F-98 glioma in rats after 7 days of treatment.⁶ An additional syngeneic, orthotopic model of non-small cell lung cancer in mice showed that 150 kHz TTF therapy significantly ($p < 0.01$) inhibited tumor growth within 7 days of treatment.^{10,11} Furthermore, the additive effect of TTF therapy with chemotherapy seen *in vitro* was recapitulated in different *in vivo* models.^{6,9} Finally, in a metastatic tumor model using a squamous carcinoma tumor implanted in the kidney capsule of rabbits, TTF therapy applied to the abdomen blocked metastatic spread of tumor from the kidney to the lungs.^{10,27}

Translating TTF Therapy into Clinical Use

Since TTF therapy is a physical antimitotic modality with no half-life, its application should be continuous. Kinetic modeling was used to predict the minimal treatment duration needed with TTF therapy.¹² Based on those data, a minimal treatment course of 4 weeks was defined and implemented in clinical studies. *In vivo* animal experiments and pilot clinical data subsequently verified the 4-week minimal treatment duration.¹² Such continuous delivery was made possible by the development of a portable, battery-operated, modular device that patients can use at home (NovoTTF-100A, Novocure, Haifa, Israel). Finally, extensive toxicity studies of TTF therapy were performed in healthy

KEY POINTS

- Tumor treating fields (TTF) therapy is an emerging, low-toxicity treatment modality for solid tumors based on the delivery of antimitotic alternating electric fields to the tumor, which interfere with cytokinesis and microtubule assembly that eventually lead to cell death.
- As a monotherapy, TTF therapy is at least as effective as currently available active chemotherapy and biologic therapies for the treatment of recurrent glioblastoma (GBM).
- The efficacy of this noninvasive treatment modality is achieved with significantly less toxicity and a better quality of life compared with chemotherapy.
- Preliminary data suggest TTF therapy acts synergistically with temozolomide and other chemotherapy in both preclinical and clinical trials.
- Future research should focus on integrating TTF therapy into the treatment of GBM in the adjuvant and maintenance settings, as well as in the treatment of other solid tumor malignancies.

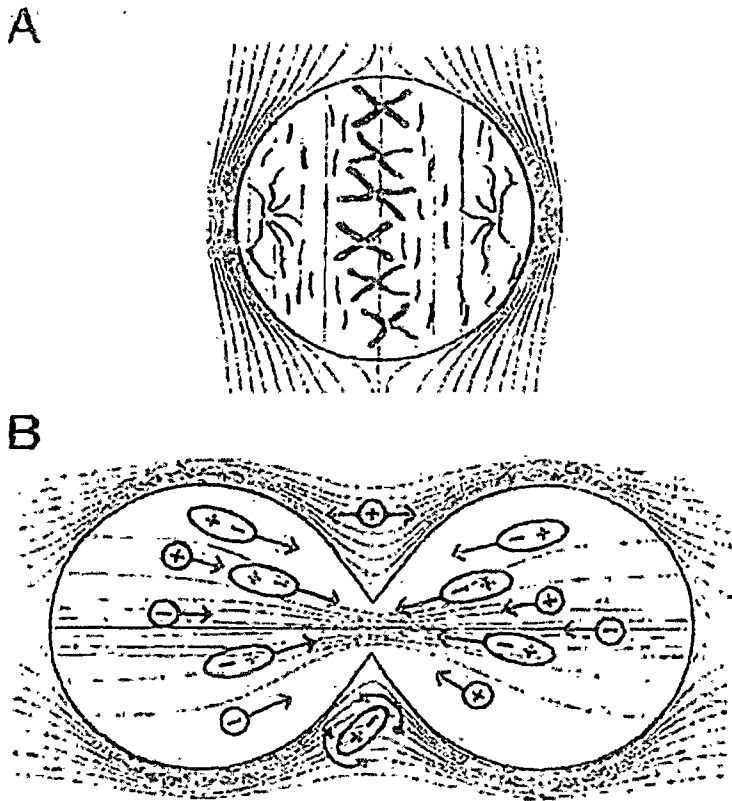


Fig. 2. Effects of tumor treating fields therapy on intracellular structures during mitosis. (A) During metaphase, tubulin dimers align with the external electric field, interfering with the formation of the mitotic spindle. (B) During cytokinesis, the nonuniform electric field formed within the dividing cell drives charged and polar macromolecules and organelles toward the cleavage furrow.

mice, rats, and rabbits.^{6,9} Clinical, laboratory, and pathologic analyses showed that TTF therapy is well tolerated and does not lead to systemic toxicity in animals. As expected by the frequency range of TTF therapy (100–300 kHz), these electric fields do not have any effect on excitable tissues (neural, muscular, or cardiac), nor do they cause significant heating.^{18–15}

Clinical Testing of TTF Therapy as a Monotherapy

The NovoTTF device was first applied to patients in a small feasibility trial in Switzerland in 2008.¹⁰ In 2004, TTF therapy was tested in a pilot clinical trial in patients with recurrent GBM (Table 3).⁶ This single-center, single-arm trial included patients with favorable prognostic character

Table 1. In Vitro Evidence Overview

Histology	Cell Line	Optimal/Effective TTF Frequency (kHz)	Additive/Synergistic with Chemotherapy ¹	Reference
High-grade glioma	F-98; C-6; RG-2	200	Tamoxifen/dacarbazine	Can Res, 2004 ³
	U-118; U-87			Proc Natl Acad Sci U S A, 2007 ⁹
Breast adenocarcinoma	Normal	120	Cyclophosphamide	Can Res, 2004 ³
	MDA-MB-231			
	MCF7		Doxorubicin	Neuro Oncol, 2011 ⁴
	Multidrug resistant	120	Paclitaxel	BMC Cancer, 2010 ⁷
	MDA-MB-231Dox			
Non-small cell lung cancer (adenocarcinoma)	AA8/EmR ¹		Doxorubicin	
	MCF7/Mx		Paclitaxel	
	H1299	150	Paclitaxel	ERS, 2010 ⁸
	LLC		Pemetrexed	AACR, 2007 ⁶
				Can Res, 2004 ³
Colorectal adenocarcinoma	CT-26	100*	NA	Can Res, 2004 ³
Malignant melanoma	B16F1 Pigella	100	NA	Can Res, 2004 ³
Prostate	PC-3	100*	NA	Can Res, 2004 ³
Cervical cancer	HeLa	200*	NA	Neuro Oncol, 2011 ⁴

Abbreviations: TTF, tumor treating fields; NA, not available (was not reported by the authors).
* Effect seen at this frequency; additional frequencies were not tested

TTF THERAPY IN GLIOBLASTOMA

Table 2. In Vivo Evidence Overview

Tumor Type	Anatomic Location	Animal Model	Frequency (hits)	Effect of TTF	References
GBM	Right hemisphere	Rat	200	Tumor growth inhibition with 2 and 3 field directions	<i>Proc Natl Acad Sci U S A</i> , 2007 ⁸
Non-small cell lung cancer	Lung parenchyma	Mouse	150	1. Tumor growth inhibition with 2 field directions 2. Additive tumor inhibition with pemetrexed	<i>ERS</i> , 2010 ⁸
Malignant melanoma	Intradermal	Mouse	100	Tumor growth inhibition with 1 and 2 field directions	<i>Can Res</i> , 2004 ⁹ <i>Proc Natl Acad Sci U S A</i> , 2007 ⁵
Malignant melanoma VX-2 (xenograft)	Intravenous Kidney capsule	Mouse Rabbit	100 150-200	Inhibition of metastatic seeding in the lungs 1. Tumor growth inhibition seen with 2 field directions 2. Increase in median survival 3. Inhibition of metastatic seeding in the lungs 4. Additive tumor inhibition with paclitaxel	<i>Clin Exp Metastasis</i> , 2009 ¹⁰ <i>Clin Exp Metastasis</i> , 2009 ¹⁰ <i>AACR</i> , 2009 ²⁷ <i>Neuro Oncol</i> , 2010 ¹²

Abbreviation: GBM, glioblastoma

istics. Treatment with the device was well tolerated, and no treatment-related serious adverse events were reported. Most patients developed grade 1 to 2 contact dermatitis beneath the transducer arrays on the scalp. Efficacy endpoints were very encouraging with a 20% objective response rate, progression-free survival (PFS) at 6 months of 50%, median time to progression (TTP) of 26 weeks, and median overall survival (OS) of 62.2 weeks (14.4 months). Compared to the historic results of salvage chemotherapy, these results showed clear activity of TTF therapy when used as a monotherapy in recurrent GBM.¹⁷

Based on the results of this pilot trial, a pivotal phase III, multicenter, randomized (1:1) clinical study was initiated in patients with recurrent GBM (Table 3). The randomized study, which recruited 237 patients between 2006 and 2009, compared the efficacy and safety of monotherapy with the NovoTTF device to that of the best available active chemotherapy according to physician's choice. Thirty-six patients received bevacizumab, 86 received nitrosureas, 12 received temozolomide, and 33 received other agents. This was the largest randomized study in recurrent GBM to be completed to date. The results of the study were presented at the 2010

ASCO Annual Meeting and were updated at the 2011 Society for Neuro-Oncology (SNO) Annual Meeting.^{18,19} Baseline characteristics of patients were balanced between the two treatment groups. In both groups, patients had poor prognostic predictors compared with previous clinical trials of recurrent GBM (90% of patients were at their second or subsequent recurrence; 20% had failed bevacizumab before entering the trial; and the average tumor diameter was above 5 cm). In the conservative intent-to-treat (ITT) analysis, the study showed that patients with recurrent GBM treated with NovoTTF alone had comparable OS to that of patients who received chemotherapy and/or bevacizumab (8.6 months vs. 6.0 months, respectively; $p = 0.26$; hazard ratio [HR] = 0.86; Table 3). Although NovoTTF did not show superiority over active chemotherapies, it was clear that it was at least as effective as these treatments. Secondary endpoints in the trial were supportive: blinded radiology review showed that PFS at 6 months was 21.4% in the NovoTTF group compared with 15.2% in the chemotherapy group ($p = 0.24$). There were more radiological responses seen in the NovoTTF group compared with the chemotherapy group (12% vs. 6%, respectively; $p = 0.07$), including

Table 3. Clinical Evidence Overview

Indication (Analysis Group)	Trial Phase (# of Subjects) Analysis	Overall Survival (Months)		Hazard Ratio (p)	Progression-Free Survival (PFS) at 6 Months or Median PFS (Weeks)		P value	References
		TTF	Chemo		TTF	Chemo		
Recurrent GBM (at first relapse)	Phase I-II (n = 10) ITT Analysis	14.5 m	6.0 m*	Non-randomized	50%	15%*	NA	<i>Proc Natl Acad Sci U S A</i> , 2007 ³
Recurrent GBM (at second and fourth relapse)	Phase III (n = 237) ITT analysis	6.6 m	6.0 m	HR = 0.86 ($p = 0.26$)	21.4%	15.2%	$p = 0.24$	<i>J Clin Oncol</i> , 2010 ¹⁸ <i>Neuro Oncol</i> , 2011 ¹⁹
Recurrent GBM (treated patients only)	Phase III (n = 210) PP Analysis	7.8 m	6.0 m	HR = 0.67 ($p = 0.012$)	26.2%	15.2%	$p = 0.03$	<i>J Clin Oncol</i> , 2010 ¹⁸ <i>Neuro Oncol</i> , 2011 ¹⁹
Recurrent GBM (KPS \geq 80, age < 61)	Phase III (n = 110) Subgroup analysis	8.8 m	6.6 m	HR = NA ($p < 0.01$)	25.4%	7.7%	NA	<i>Neuro Oncol</i> , 2010 ¹⁹
Recurrent GBM (after bevacizumab failure)	Phase III (n = 43) Subgroup analysis	4.4 m	3.1 m	$p = 0.02$	NA	NA	NA	<i>Neuro Oncol</i> , 2010 ²⁰
Recurrent GBM (TTF versus bevacizumab)	Phase III (n = 156) Subgroup analysis	6.6 m	5.0 m	HR = 0.65 ($p = 0.048$)	21%	21%	$p > 0.05$	<i>Neuro Oncol</i> , 2011 ²¹
Newly diagnosed GBM (together with temozolomide)	I-II (n = 10) ITT Analysis	39+ m	14.7 m*	$p = 0.002$	90%	50%*	NA	<i>BMC Med Phys</i> , 2009 ⁸
Relapsed advanced NSCLC (together with pemetrexed)	I-II (n = 42) ITT Analysis	13.8 m	8.2 m*	NA	28 w	12 w*		<i>ESMO</i> , 2010 ²⁵ <i>ERS</i> , 2010 ⁸ <i>Expert Opin Investig Drugs</i> , 2010 ¹¹

Abbreviations: GBM, glioblastoma; ITT, intention to treat; NA, not available (was not reported by the author); HR, hazard ratio; PP, per protocol; KPS, Karnofsky performance status; TTF, tumor treating fields; NSCLC, non-small cell lung cancer.
* Single-arm trials with literature control

three sustained complete responses in the NovoTTF group compared with none in the chemotherapy group. These results were accompanied by significantly ($p < 0.05$) less treatment-related adverse events with NovoTTF compared with chemotherapy. Patients in the NovoTTF group reported a higher quality of life compared with patients treated with chemotherapy. This analysis was based on the European Organisation for Research and Treatment of Cancer QLQ-C30 and mirrored the lack of chemotherapy-related toxicities in the NovoTTF group. Interestingly, patients in the NovoTTF group reported better cognitive and emotional functioning and much less pain than patients in the chemotherapy group, although these domains of the questionnaire are not related to known side effects of chemotherapy.

To date, several exploratory analyses of the study data have been performed. The first analysis compared patients who received the same "amount" of therapy in both groups. This prospectively defined per-protocol analysis excluded patients from both groups who received less than one pre-defined treatment course. The analysis demonstrated superior survival in the NovoTTF group compared with the chemotherapy group (7.8 months vs. 6.0 months; $p = 0.012$, HR = 0.67).^{16,19} The rationale behind this analysis is that TTF is a physical modality with no half-life, so that the moment the therapy is stopped, its antimetabolic effect stops as well. In contrast, chemotherapies have measurable plasma and tissue half-life, which results in continued efficacy and toxicity long after a dose has been given. Therefore, to achieve pharmacokinetic balance in the "amount" of treatment in both groups, this analysis used a simplified criterion that one course of chemotherapy (e.g., 1 day of carmustine or 5 days of temozolomide) is equivalent to four weeks of continuous TTF therapy.

Two more analyses of the study data were presented at the 2010 and 2011 SNO Annual Meetings.^{20,21} The first study analyzed known clinical prognostic factors of age and Karnofsky performance status (KPS). This analysis demonstrated that in patients age 60 and younger with a KPS greater than 70, treatment with NovoTTF resulted in superior OS compared with chemotherapy (6.8 months vs. 6.6 months; $p < 0.01$). This survival advantage could be attributed to better compliance with TTF therapy in this group of patients. In support of this finding, a statistically significant correlation was seen in the NovoTTF group between treatment compliance (as measured by the device computerized log file) and OS ($p = 0.0476$).

The second analysis is a post hoc, exploratory analysis of the treatment of 120 patients with NovoTTF compared with 36 patients with bevacizumab. Although without a prespecified analysis in the trial, patients in the study treated with NovoTTF lived significantly longer than those treated with bevacizumab (6.6 months vs. 5.0 months, respectively; $p = 0.048$, HR = 0.95).²¹ This analysis included all TTF patients who received either bevacizumab or NovoTTF. Patient characteristics were almost identical and, in fact, favored the bevacizumab group prognostically. Clearly, this analysis cannot be taken as final evidence of superiority of NovoTTF over bevacizumab; however, it should be treated as hypothesis-generating data for future clinical studies. Finally, in the 43 patients who entered the study after bevacizumab therapy failure (approximately 30% of patients in both groups), OS was significantly longer with TTF therapy

than with chemotherapy (4.4 months vs. 3.1 months, respectively; $p = 0.02$). The data for the chemotherapy-treated group is in line with previous publications, which showed that following bevacizumab failure, the survival of patients with recurrent GBM is limited.²²

Based on the results of this pivotal phase III study, the FDA approved the NovoTTF-100A device on April 8, 2011, through the premarket approval (PMA) regulatory pathway. The PMA pathway is reserved for class III (high-risk) medical devices and requires preclinical, clinical, and manufacturing evidence, including review of both efficacy and safety data by a panel of independent experts. The FDA concluded that the study results showed NovoTTF to be comparable in efficacy to active chemotherapy, without many of the side effects associated with chemotherapies and with a better quality of life.²³

Clinical Trials Evaluating TTF Therapy in Combination with Chemotherapy

Two studies of combined TTF therapy and chemotherapy have been published to date. The first was a single-arm, single-center trial performed in 2008 in patients with newly diagnosed GBM.¹⁹ Patients received the Stupp protocol with TTF therapy added to maintenance temozolomide.²⁴ This trial showed promising PFS and OS data (PFS > 14 months; OS > 39 months; Table 3) and served as the basis for an ongoing, multicenter, pivotal phase III, randomized clinical study comparing TTF therapy and temozolomide with temozolomide alone in the maintenance stage of the Stupp protocol.

The second study tested TTF therapy together with pemetrexed in 42 patients with pretreated, advanced non-small cell lung cancer.^{8,11,25} Efficacy and safety with this combined treatment paradigm were promising. Time to local disease progression in the lungs and liver (where TTF was applied) was 28 weeks, and OS was 13.8 months. In contrast, TTF and OS for pemetrexed alone were previously reported to be 12 weeks and 8.3 months, respectively.²⁶

TTF therapy is still in its early days. However, it has an established mechanism of action, and a growing body of preclinical evidence has shown its wide applicability in solid tumor malignancies either alone or in combination with standard chemotherapies. Objective antitumor activity and an unprecedented safety profile of this treatment modality have been seen in patients with recurrent GBM. Although TTF monotherapy has been shown to be at least as effective as the best available chemotherapies today for recurrent GBM, in-depth analysis of the phase III study data identified at least two subgroups where TTF therapy was superior to chemotherapy and could be offered to patients as an alternative to chemotherapy: younger patients with a better functional status and patients in whom bevacizumab treatment has failed in the past.

Conclusion

The approval of TTF therapy for recurrent GBM ushers in a fourth modality of cancer treatment. More importantly, TTF treatment has a superior safety profile, and its minor side effects do not appear to overlap with those of cytotoxic chemotherapies, targeted agents, or antiangiogenesis drugs. Therefore, the rational combination of TTF therapy with specific pharmacologic agents may enhance tumor cell death

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because of potential additive or synergistic effects. First, as demonstrated in preclinical and clinical models, chemotherapy administered together with 'TTF' therapy may result in additive or synergistic tumor control without increasing systemic toxicities. Second, TTF treatment could be combined with targeted agents that block survival signaling within the tumor cell. This block may be sufficiently strong to enhance the cytotoxic effect of TTF therapy or vice versa.

Third, the combination of TTF and antiangiogenesis agents may be another promising path that combines different antitumor treatments to improve tumor control. Lastly, the proper scheduling of TTF therapy with other agents is unknown. Additional research may shed light on the optimal scheduling that may achieve a synergistic effect on tumor growth leading to long-term tumor control and enhanced patient survival.

Authors' Disclosures of Potential Conflicts of Interest

Author	Employment or Leadership Positions	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors

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We have recently shown that low intensity, intermediate frequency, electric fields inhibit by an anti-microtubule mechanism of action, cancerous cell growth *in vitro*. Using implanted electrodes, these fields were also shown to inhibit the growth of dermal tumors in mice. The present study extends these findings to additional cell lines [human breast carcinoma; MDA-MB-231, and human non-small-cell lung carcinoma (H1299)] and to animal tumor models (intradermal B16F1 melanoma and intracranial F-98 glioma) using external insulated electrodes. These findings led to the initiation of a pilot clinical trial of the effects of TTFs in 10 patients with recurrent glioblastoma (GBM). Median time to disease progression in these patients was 26.1 weeks and median overall survival was 62.2 weeks. These time to disease progression and OS values are more than double the reported medians of historical control patients. No device-related serious adverse events were seen after >70 months of cumulative treatment in all of the patients. The only device-related side effect seen was a mild to moderate contact dermatitis beneath the field delivering electrodes. We conclude that TTFs are a safe and effective new treatment modality which effectively slows down tumor growth *in vitro*, *in vivo* and, as demonstrated here, in human cancer patients.

cancer | glioblastoma | tumor treating fields

Because living cells consist of ions, polar or charged molecules, membranes, and organelles, they are responsive to and often generate electric fields and currents. The electric activity of cells plays a key role in many essential biological processes. The electric fields associated with all of the above phenomena are in the range of 0–10 V/cm, except within cell membranes (1) where they may reach 10^3 V/cm. Whereas electric fields induce ion flow, polar molecules only orient themselves along the lines of a uniform field (2). However, nonuniform electric fields exert forces on polar molecules forcing them to move toward higher field intensity, a well known process known as dielectrophoresis (3, 4). Electric fields and resulting currents, when sufficiently large, stimulate nerves, muscles, cardiac muscle, etc. Only much larger fields generate heat that may damage cells (5).

In an electric field of alternating direction (ac field) all charges and polar molecules are subjected to forces of alternating direction so that ionic flows and dipole rotation oscillate (Fig. 1). In view of the relatively slow kinetics of the bioelectrical responses, as the ac fields frequency is elevated, their biological effect (except for heating) is reduced such that, >10 kHz, it becomes negligible. Therefore, it is generally believed that ac fields of 100 kHz or above have no meaningful biological effects (5), although a number of nonsignificant effects have been described (6–8).

In contradiction to this belief, we have recently demonstrated (9) that 100 kHz to 1 MHz ac fields have significant specific effects on dividing cells. The basis of these effects during cytokinesis was shown to be the unidirectional forces induced by

the inhomogeneous fields at the bridge separating the daughter cells (Fig. 1B) that interfere with spindle tubulin orientation and induce dielectrophoresis.

It is the aim of this work to further study the effects of ac fields on quiescent and proliferating cells in culture, animal cancer models, and cancerous tumors in humans. Following a basic work on cell cultures (9), we demonstrate here that such fields, termed tumor treating fields (TTFs), are effective when applied by insulated external electrodes to animal cancer models and patients with recurrent glioblastoma (GBM). In a pilot clinical trial conducted on this extremely malignant tumor of glial cell origin (10, 11), TTFs treatment was found to be both safe and effective in slowing tumor progression. These promising results raise the possibility that TTFs could become a new treatment modality for cancer.

Cells in Culture

The effects of a 24-h exposure of four of the most common types of cancer [malignant melanoma, glioma (part of the data for malignant melanoma and glioma cells was taken from ref. 9), breast carcinoma, and non-small-cell lung carcinoma to TTFs] are illustrated in Fig. 2. It is seen that the number of unexposed (control) cells roughly doubles every 24 h, whereas the proliferation rate of the exposed cells is slowed down during exposure and gradually recovers after treatment is terminated (Fig. 2A). The frequency dependency of the effects is depicted in Fig. 2B. It is seen that the optimal frequency is 100 kHz for mouse melanoma (B16F1), 150 kHz for human breast carcinoma (MDA-MB-231), and 200 kHz for rat glioma (F-98). In addition, similar experiments were performed in two human glioma cell lines (U-118 and U-87). In both, the optimal TTFs frequency was identical to rat glioma cell lines (i.e., 200 kHz).

The "dose-response curve," i.e., the relationship between the TTFs effects and field intensity, is given in Fig. 2C. It is seen that effect on cell division and cell death (by apoptosis) is intensity dependent, the sensitivity being highest for mouse

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Conflict of interest statement: Y.P. has a minority holding in NovoCure Ltd. and is a member of the company board of directors; E.D.K., A.L., D.M., S.S.-S., Z.G., R.S., and Y.W. are employed in full or part by NovoCure Ltd.; and M.S. is a clinical trial consultant to NovoCure Ltd.

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Abbreviations: FEM, finite element mesh; GBM, glioblastoma; OS, overall survival; PFS, progression-free survival at 6 months; TTFs, tumor treating fields; TTP, time to disease progression.

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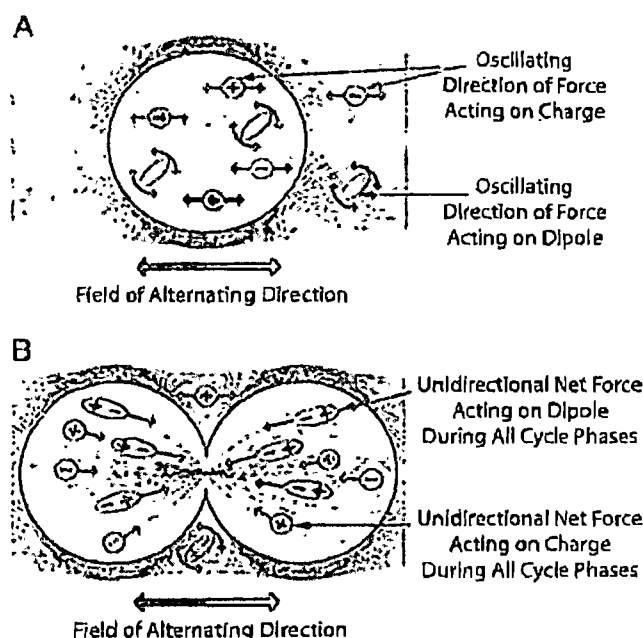


Fig. 1. ac field distribution in and around quiescent (A) and dividing (B) cells. Inside quiescent cells, the field is uniform, and the oscillating electric forces result only in "vibration" of ions and dipoles (the forces associated with each half cycle are denoted white and gray arrows). In contrast, the nonuniform field within dividing cells (B) induces forces pushing all dipoles toward the furrow. Note that at frequencies of 0.1–1.0 MHz, the cell membrane impedance is relatively high, so only a small fraction of the currents penetrate the cells as seen from the density of lines.

melanoma cells, decreasing for rat glioma and for human non-small-cell lung carcinoma and lowest for human breast carcinoma.

From the mechanism of action of TTFields, as illustrated in Fig. 1, it can be deduced that their efficacy must be a function of the angle between the field and axis of division; when the two are parallel its maximal and when one is perpendicular to the

other, it must be minimal. Because in culture the axis of division is randomly oriented, only a fraction of the dividing cells are subjected to optimal treatment. To overcome this problem, multiple field directions were applied sequentially every 0.25–1 sec. Two perpendicular fields were found to be ~20% more effective than the single-direction one for B16F1 and F-98 cells. This result is consistent with the previously reported effects on malignant melanoma cells (9).

Animal Tumor Models

Intracranial Glioblastoma. Our report (9) described the effects of TTFields applied by means of implanted electrodes to intracranial malignant melanoma in mice. This report compares 40 Fischer rats inoculated intracranially with glioma cells, treated by means of external electrodes with a temperature, and geometry matched electrode control group. The treatment duration was 6 days, using the optimal frequency of 200 kHz (see Fig. 2) at 2 V/cm. Fig. 3 depicts the computed field distribution in the rat brain (Fig. 3A), exemplary posttreatment MRI images of a control (Fig. 3B) and a treated tumor (Fig. 3C). The maximal diameter of the treated tumor is about half that of the control one.

The average inhibitory effect of unidirectional TTFields (in a temporal-temporal direction) was small and did not reach statistical significance (treated tumor volume 19.8% smaller than sham control tumors; $n = 26$; $P = 0.19$, Student's t test). However, increasing the number of TTFields directions caused statistically significant inhibition of tumor growth, reaching 42.6% and 53.4% for two ($n = 42$; $P < 0.01$, Student's t test) and three ($n = 10$; $P < 0.01$, Student's t test) directions positioned at 45–90° to each other, respectively.

Frequency Dependence of the Inhibitory Effect of TTFields. The TTFields inhibitory efficacy vs. frequency was studied on mice inoculated with B16F1 melanoma. The mice ($n = 26$) were treated for 5 days by single-direction TTFields of different frequencies. The maximal growth inhibition was found at 100 kHz, with the treated tumor size $62.7 \pm 8.9\%$ that of control tumors. Although this frequency dependence *in vivo* did not reach statistical significance (single-factor ANOVA, $P = 0.11$), it shows the same frequency dependency as the dependence of cultured B16F1 cells reported in ref. 9, which supports the

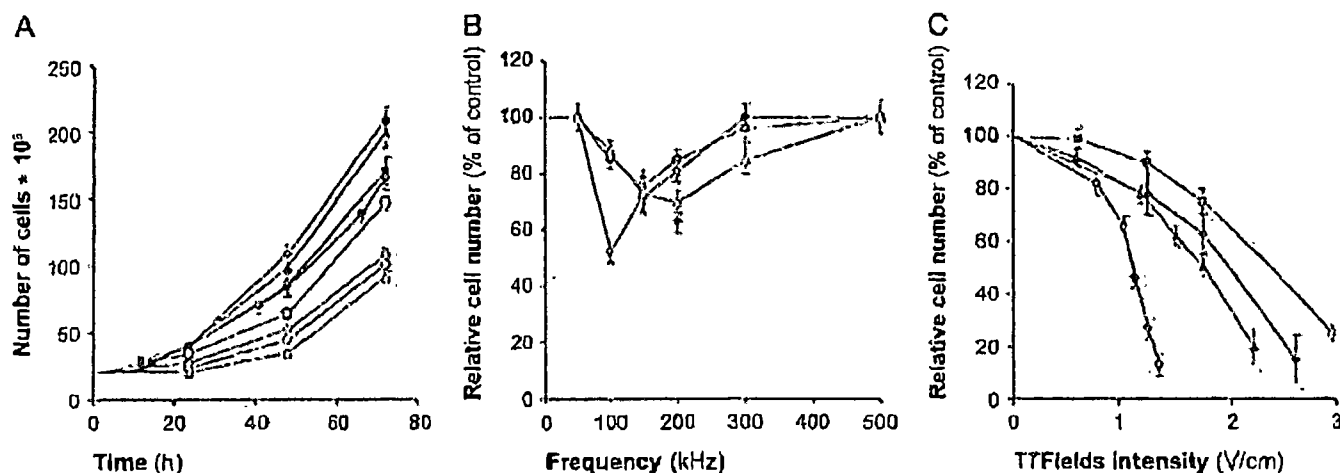


Fig. 2. Time, frequency, and intensity dependence of the effect of TTFields on cancer cell proliferation. (A) The number of cells in untreated cultures (filled symbols) as compared with cultures treated with TTFields (open symbols) for 24 h (1.75 V/cm for MDA-MB-231, F-98, and H1299 cells and 1.1 V/cm for B16F1 cells). (B) The relative change in number of cells after 24 h of treatment of different frequencies (same TTFields intensity). (C) The effect of 24 h of exposure to TTFields of increasing intensities (at optimal frequencies). \bullet and \circ , B16F1; \blacksquare and \square , MDA-MB-231; \blacktriangle and \triangle , F-98; \blacklozenge and \lozenge , H1299.

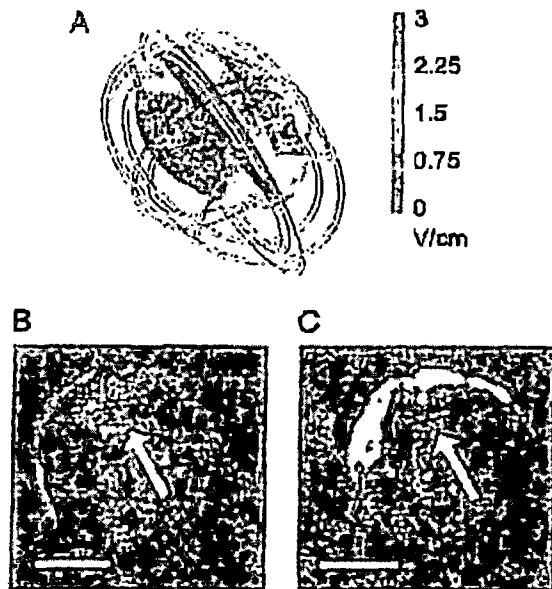


Fig. 3. TTFIELDS inhibition of the growth of intracranial glioma. (A) FEM simulations (using a three-dimensional mesh) of the distribution of TTFIELDS intensity within a simplified rat brain model. (B and C) Exemphary T1 weighted coronal MRI sections (after IV injection of Gd-DTPA) of the heads of a control and a TTFIELDS treated (200 kHz, two-directional TTFIELDS) rat, respectively. In both examples, the section shown is that with the largest diameter tumor. Head simulations are 3.1×1.9 cm ellipsoid; skin thickness, 0.4 mm ($\sigma = 0.00045$ S/m; $\epsilon = 1,120$); skull thickness, 1.1 mm ($\sigma = 0.0155$ S/m; $\epsilon = 16$); thickness of the CSF surrounding the brain, 0.5 mm ($\sigma = 2.5$ S/m; $\epsilon = 109$); and brain itself has the properties of a uniform white matter ($\sigma = 0.15$ S/m; $\epsilon = 3,200$). The electrodes placed over a 0.5-mm layer of hydrogel. Note the almost uniform field intensity in most brain volume. (Scale bars, 1 cm.)

conclusion that this is the optimum frequency. In contrast, rats bearing intracerebral glioma were unaffected by 100 kHz TTFIELDS, whereas 200 kHz TTFIELDS caused significant inhibition of tumor growth.

Safety Profile of TTFIELDS in Healthy Animals. TTFIELDS (100 kHz) at 6 V/cm were applied to the chest of three New Zealand rabbits. No changes were seen in the rate or regularity of cardiac rhythm

throughout and following the exposure. To test the safety of chronic TTFIELDS application TTFIELDS were applied to either the head ($n = 30$, 1 V/cm for 4 weeks) or the chest ($n = 10$, 3 V/cm for 2 weeks) of New Zealand Rabbits. All animals were assessed weekly for weight, temperature, ECG, CBC, wide chemistry panel and coagulation. After a 1-month follow-up period, all animals were killed and had samples of major organs examined by a pathologist. No treatment-related toxicities were recorded in any of the animals.

GBM Patients

TTFIELDS Treatment of Patients with Recurrent GBM Brain Tumor. Ten patients with recurrent GBM were included in the trial (see *Materials and Methods* and supporting information (SI) Table 1).

As seen in Fig. 6A, the median time to disease progression (TTP) of the patients is 26.1 weeks (range 3–124 weeks) and the progression-free survival at 6 months (PFS6) is 50% (23–77%; 95% confidence interval). Two of the patients were still progression free at study closure.

The median overall survival (OS) of TTFIELDS treated patients is currently 62.2 weeks (range 20.3–124.0 weeks). These TTP and OS values are more than double the reported medians of historical control patients. Three of the patients are still alive at this time. The Kaplan-Meier survival curve (12) of the treatment results is shown in Fig. 4B.

The TTFIELDS treatment resulted in one complete response (Fig. 5A) which is still tumor free per MRI ten months after stopping treatment and one partial response (Fig. 5B) that is still responding 7 months after stopping treatment. Both are still progression free >2 years from treatment initiation. In addition one patient had minimal response and four had stable disease for over 4 months before progressing.

Safety Profile of TTFIELDS Applied to GBM Patients. The 10 recurrent GBM Patients received treatment for a total of 280 weeks without a single treatment-related serious adverse event and no significant changes were seen in serum chemistry or blood count in any of the patients. The only changes seen consistently were elevated liver enzymes, attributed to anti-epileptic drug usage. Two patients had partial seizures that were unrelated to treatment. Nine of ten patients suffered from a mild to moderate contact dermatitis beneath the electrode gel. This treatment-related adverse event responded well to application of steroid creams and periodic electrode relocation.

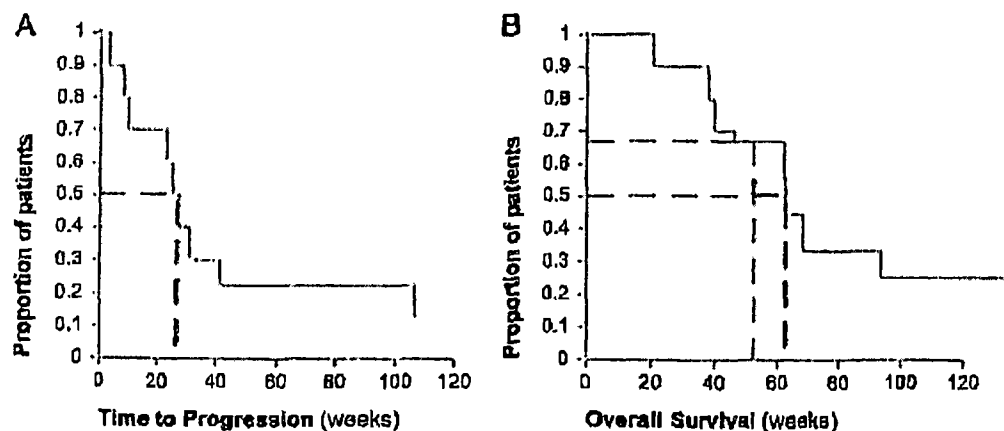


Fig. 4. Efficacy of TTFIELDS treatment in recurrent GBM. (A) TTP of treated patients ($n = 10$); median TTP is 26.1 weeks (dashed black line). (B) Kaplan-Meier OS curve for NovaTTF-100A treated patients ($n = 10$). The median OS in these patients is 62.2 weeks (black dashed line), and the 1-year survival rate is 67.5% (blue dashed line).

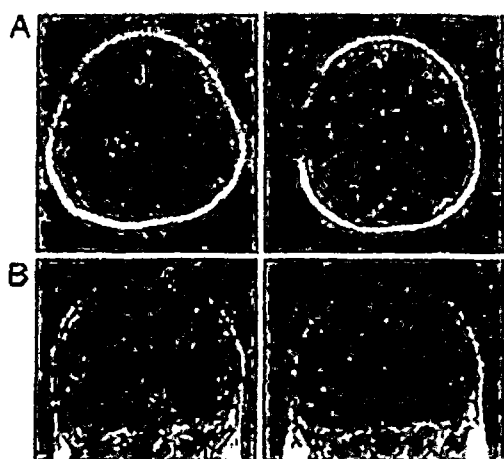


Fig. 5. Exemplary T1-weighted, post contrast, MRI scans of recurrent GBM patients before (Left) and after (Right) TTFIELDS treatment. (A) Complete response after 8 months of treatment. (B) Stable disease (10% reduction in contrast enhancing area) after 9 months of treatment.

Discussion

Alternating electric fields have been shown to have a wide range of effects on living tissues. At very low frequencies (<1 kHz), electric fields stimulate excitable tissues through membrane depolarization (13) and have been claimed to stimulate bone growth and accelerate fracture healing (14). However, as the frequency of the electric field increases the stimulatory effect diminishes, whereas above MHz a completely different biological effect, tissue heating, becomes dominant (15, 16).

Alternating electric fields of intermediate frequencies (10 kHz to 1 MHz) were considered not to have any meaningful non-thermal biological effects (5). An exception, are the TTFIELDS described in ref. 9. This presumed lack of effect of such fields is consistent with the fact that when electric fields, that exert forces only on charges and dipoles reverse direction at a high frequency, their net effect tends to null out. Thus, the effects were minor and have neither been shown to be beneficial or detrimental to humans (5, 8, 17).

In this study we try to use TTFIELDS as a new cancer treatment modality. We first extended the *In-Vitro* study of TTFIELDS effect on glioma and melanoma cells (9) to several of the most prevalent cancers; breast carcinoma and non-small-cell lung carcinoma. It was found that the proliferation of these cells is arrested and the cells are destroyed (Fig. 2). The optimal frequencies differed between cancer cell types. To understand this finding we calculated the force on a 1 μ m polarizable spherical particle in a dividing cell as function of cell radius, membrane thickness and cytoplasm conductivity. It was found that optimal TTFIELDS frequency is inversely related to cell size (see *SI Appendix A*) in a way consistent the diameter variability of the different cell types studied.

In the previous study (9) animal treatment was done by using implanted electrodes. In the present study, we used the much more practical externally applied electrodes. Furthermore, as the available data suggests that treatment may need to be prolonged, the use of conducting electrodes may result in serious problems: local damage to the skin because of electrolysis and the generation of free radicals at the electrode-tissue interface, skin permeabilization by the transdermal currents (18, 19), and calcium accumulation within cells (20) that can result in cell death (21). Clearly, the first 2 adverse effects do not occur at the surface of insulated electrodes. Using fluorescence calcium imaging techniques, we could demonstrate that electric field

induced calcium accumulation is eliminated by the use of insulated electrodes (see *SI Appendix B*). However, the large potential drop across the insulation high impedance poses a serious problem; to generate the fields of the required intensity potentials of $>1,000$ V must be used. As such high voltages may compromise patient safety, low impedance electrodes were developed. The impedance of insulation is lowered by using an insulating material, lead magnesium niobate-lead titanate (PMN-PT) (EDO, New York, NY), that has a dielectric constant of $\epsilon > 5,000$. Under these conditions the electrodes have a capacitance of ~ 10 nF/cm², i.e., an impedance of 100–200 Ω at the TTFIELDS frequency range. Thus, only 50% of the applied voltage is lost on the insulation in the mice experiments. The corresponding potential drop on the 22.5 cm² electrodes placed on the patient's head, in the trial presented here, is only $\sim 10\%$ of the applied voltage.

A major limitation of all current cancer treatments is their unfavorable therapeutic index. Two types of toxicities may be expected from an electric field based treatment. First, the fields could theoretically affect excitable tissues causing cardiac arrhythmias or seizures. However, such effects are not expected to occur, because for sinusoidal alternating fields of >10 kHz, excitation of nerves and muscles decreases dramatically, because of the parallel resistor-capacitor nature of the cell membrane (22). Indeed, in both acute and chronic application of TTFIELDS to animals and patients, there was no trace of abnormal cardiac or neurological activity. Secondly, TTFIELDS might be expected to damage rapidly dividing normal cells within the body, i.e., bone marrow and small intestine mucosa. However, no treatment-related toxicities were found in any of the treated patients or upon animal exposure to field intensities threefold higher than the effective anti-tumoral dose. With regards to hematopoiesis the reason for this is that these cells, which reside mainly in the bone marrow, are protected from the TTFIELDS by the high impedance of both the bone and bone marrow (23). This was demonstrated by calculating the TTFIELDS distribution in an extremity, such as a leg, by using the finite element mesh (FEM) method. It was found that the field intensity is 100-fold lower within the bone marrow compared with the surrounding tissues. The lack of damage to intestinal mucosa probably reflects that the small intestine mucosal cells have a slower replication cycle than neoplastic cells (24) and that the intestine changes its orientation, relative to the applied field, often lowering the efficacy of the mitotic disruption.

The tumor inhibitory effect of TTFIELDS has been attributed previously to two separate mechanisms (9): interference with the formation of the mitotic spindle microtubules and physical destruction of cells during cleavage, both of which are strongly dependant on the orientation of mitosis axis versus the field vectors. Because the relative orientation of the mitosis axis during cytokinesis is random, it would be expected that only a fraction of dividing cells would be affected by TTFIELDS of any specific direction. To overcome this problem, we applied sequentially several field directions and have shown that increasing the number of directions from 1 to 3, resulted in a significant increase in the anti-proliferative efficacy of TTFIELDS *in vitro* and *in vivo*.

Following encouraging evidence from experimental animals, a clinical trial of the effect of TTFIELDS on patients with recurrent GBM was initiated. Because *in vitro* data indicate that TTFIELDS are most effective when applied for >16 h continuously (data not shown), patients were treated daily for an average of 18 h per day until progression. The results reported here are the first evidence of the safety and efficacy of TTFIELDS used to treat cancer in patients. Preliminary accounts of this data were published in

abstract form.¹¹³⁶⁷⁰ Because this was a pilot trial there was no randomized control group and the results were evaluated by comparing to historical control data. Most historically controlled pilot studies in recurrent GBM are compared with a large metaanalysis performed by Wong *et al.* in 1999 (10) and to this data we added the four prospective trials (25–28), which included >50 GBM patients, performed since that date. The average historical PFS6 based on the above studies is $15.3 \pm 3.8\%$, and the average historical TTP is 9.5 ± 1.6 weeks. OS averaged 29.3 ± 6 weeks (see S1 Table 2). When compared with these outcomes, the efficacy data collected in the current pilot trial is extremely promising (TTP, 26.1 weeks; PFS6, 50%; and OS, 62.2 weeks). These results were not accompanied by hematological or gastrointestinal toxicities, epileptic seizures, cardiac arrhythmias, etc., despite >70 months of cumulative treatment. The only side effect detected was contact dermatitis beneath the electrodes. This reaction is most likely the result of a combination of factors, including chronic moisture, heat, and occlusion of the skin; chemical irritation by constituents of the hydrogel and medical tape (29); and possibly inhibition of cellular replication in the skin by the TTFields. Thus, in conclusion, this treatment modality was well tolerated and caused almost no toxicity at all.

In summary, we demonstrated initially that TTFields are effective in arresting the proliferation and inducing death in a wide range of tumor cells in culture as well as solid tumors in animals. On this basis a clinical trial was carried out treating human patients suffering from recurrent GBM, a malignant brain tumor. It was demonstrated that the TTFields inhibit the growth of this highly treatment-resistant tumor by using special insulated electrodes, with little or no side effects. Can we expect to have similar efficacy on other human tumors? The fact that in cultures and animal models TTFields were found to be effective on all cells and tumors tested is definitely encouraging. Furthermore, TTFields being a physical, rather than chemical, modality, their efficacy is likely to be highly insensitive to specific interactions with tumor and patient receptors and other characteristic elements. Thus, like irradiation, they have the potential to be effective over a wide range of tumors. However, from the above it is apparent that their practical specificity to cancerous cells is significantly higher than that of irradiation, the therapeutic efficacy of which is often severely limited by toxicity. Therefore, we believe that there is a high probability that TTFields may prove to be an effective and safe therapeutic modality to a large number of human cancers.

Materials and Methods

Cell Cultures. Cell cultures were grown in DMEM plus 10% FCS media in a CO₂ incubator (5% CO₂) at 37°C. Cell suspension (200 μ l; total 20×10^3 cells) were placed as a drop in the centre of 35-mm Petri dishes, incubated for 24 h and then the cell number was estimated by using standard XTT method (Cell proliferation assay Kit, Biological Industries Ltd., Israel) and expressed as OD₄. Temperature was measured by a thermocouple (Omega, Stamford, CT) placed at the center of the dish. Two pairs of electrodes, insulated by a high dielectric constant ceramic (lead magnesium niobate–lead titanate (PMN-PT)), positioned in the petri dish perpendicular to each other were connected to a sinusoid function generator and amplifier. Two-directional fields were generated sequentially (1) by switching the output of the amplifier between two pairs of electrodes every

0.25–1 sec. The electric field intensity in the culture medium was measured as described in ref. 1.

At the end of 24 h of treatment, the cell number was measured by using the XTT method and expressed as OD₄. The rate of cell proliferation was expressed as the OD₄/OD₀ ratio.

Animal Models. Tumor inoculation and in vivo size assessment. Animal experiments were conducted after approval by the Technion-Israel Institute of Technology committee for the care of laboratory animals. Intracranial glioma (F-98) was inoculated stereotactically into the subcortical white matter in the right hemisphere of Fischer rats (Harlan Laboratories, Israel) by using a modification of the method described in refs. 30 and 31. Briefly, a hole, 1 mm in diameter, was punched through the scalp, 2 mm to the right of the midline and 4 mm rostral to the line connecting the external ear canals. A 0.5 mm burr hole was drilled in the bone at same location and a 26G needle was inserted to a depth of 7 mm beneath the scalp surface. Five microliters of saline containing 2.5×10^5 F-98 cells was then injected by using a microsyringe operated by a micromanipulator. The needle was left in position for 60 sec and then retracted slowly at a rate of 2 mm/min. Rats were allowed to recuperate for 24 h before treatment initiation. Tumor volume was assessed based on serial (2-mm interval) T1 weighted axial MRI images (0.5 Tesla MKI; Gyrex orbital coil; Elscint, Haifa, Israel) obtained 10 min following injection of 0.7 ml of Gadolinium (Magnevist; Soreq Radiopharmaceuticals, Yavne, Israel) into the tail vein. Tumor volume was assessed by calculating the area in square millimeters of the contrast enhanced lesion in each section. In view of the small size of the head of the rat, only three electrodes could be positioned on it, generating one to three different field directions.

Computation of the distribution of electric fields generated by external insulated electrodes. The distributions of the alternating electric field generated by external electrodes within the brains of rats were estimated by using FEM simulations. These field distributions are determined by the geometry and electrical properties of the electrodes and tissues. On average, the capacitance of each electrode is 8 nF. This translates into an impedance of 190 and 95 Ω at 100 and 200 kHz, respectively. Because the impedance of the rat head is on the order of 400 Ω , when applying 42 V, 200 kHz TTFields to rats, 14-V drop on the insulation of both electrodes and the remaining 28 V on the rat itself. The fields generated in the areas of interest are in the range of 1–2 V/cm. The calculated field distribution for the rat head is given in Fig. 3A.

Human GBM Trial. GBM patient eligibility and characteristics. Twelve patients, suffering from the brain tumor GBM were enrolled to the study. Patients eligible for enrollment had recurrence based on Macdonald criteria (32), were >18 years old, had histologically established GBM (World Health Organization grade IV), had a Karnofsky performance scale ≥ 70 , and were at least 4 weeks from any brain surgery and at least 8 weeks from radiotherapy. Patients could be at any recurrence and may have received other salvage therapies before enrollment. All patients had received adjuvant Temozolomide for their primary tumor. No concomitant chemotherapy was allowed. Multifocal disease was allowed. Patients with significant comorbidities, intracranial tumors, implanted pacemakers or documented clinically significant arrhythmias, were excluded from the trial. During review of the histology from postprogression debulking surgery, one patient was excluded from efficacy analysis because of failure to meet histological criteria for grade IV glioma. An additional patient dropped out of the trial immediately following the baseline visit because of withdrawal of consent. Individual patient characteristics are listed in S1 Table 1.

¹¹³⁶⁷⁰Kliron, E. D., Dbaly, V., Hochlitz, C., Tovary, F., Solzberg, M., Palti, Y., AACR Meeting Abstracts, April 5, 2005, Washington, DC, Abstract 5259.

⁵⁹Dbaly, V., Kliron, E. D., Palti, Y., Gutin, P.H., Congress of Neurological Surgeons, October 13, 2005, Boston, MA (abstr.).

¹¹³⁶⁷⁰Gutin, P., Kliron, E., Palti, Y., Dbaly, V., International Brain Tumor Research and Therapy Meeting, April 26, 2005, Napa Valley, CA (abstr.).

The clinical trial. A single arm, pilot trial of the safety and efficacy of TTFields treatment was performed in 10 patients with recurrent GBM. Written informed consent was obtained from each subject. The trial was performed after approval by the Na Homolce Institutional Review Board and the Czech Ministry of Health. Efficacy analysis was performed for 10 recurrent GBM patients by comparing TTP, PFS6, and OS in recurrent GBM patients treated with the NovoTTF-100A device with the TTP, PFS6, and OS of recurrent GBM patients in a literature based historical control group (10, 25–28). No statistical hypothesis testing was planned because of the small sample size. Ninety-five percent confidence intervals of survival proportions were calculated from Kaplan–Meier survival curves, by using standard formulae (33).

Measurement and simulation of TTFields intensity within the human brain. To plan the TTFields intensity necessary to treat patients with intracranial tumors, we performed FEM simulations of the intensity distribution of TTFields within a three-dimensional model of the human head. Field intensity was slightly higher in the cortex than in the center of the brain (by $\approx 30\%$), but effective (1–2 V/cm) TTFields could be generated at the center of the brain by applying ≈ 50 V to surface electrodes placed on the scalp. To validate these findings, TTFields intensity was measured within the brain of a volunteer undergoing surgery because of obstructive hydrocephalus because of a huge meningioma of the pineal region. The study was performed according to an experimental protocol approved by the Rambam Medical Center ethics committee. The measured TTFields intensity was accurate within 10% of the FEM simulated values.

TTFields treatment of GBM patients. TTFields were applied to recurrent GBM patients by using the NovoTTF-100A device (NovoCure Ltd., Haifa, Israel). This portable battery-operated device generates TTFields in GBM patients by means of insulated electrodes placed on their shaved scalps. The area of each

insulated electrode array used was 22.5 cm². Fields of 1–2 V/cm were generated by controlling the current density through the electrodes < 31 mA/cm² RMS, approximately one-third of the level that is generally recognized to present a risk of skin injury (100 mA/cm²) (34). In addition, the maximal power density beneath the electrodes was kept beneath 0.22 W/cm², i.e., below the level associated with thermal skin injury (35). Electrode temperature was monitored and the power was lowered automatically when the temperature of any electrode exceeded 41°C. This value is well below the threshold of 44°C, i.e., the lowest prolonged temperature that can cause thermal injury (34).

TTFields having the optimal frequency of 200 kHz for rat and human gliomas (see Fig. 2) and an intensity of 1–2 V/cm (peak) were used in the trial. TTFields were switched sequentially every 1 sec between two perpendicular directions; lateral and anterior–posterior, through two sets of insulated electrode pairs. Patients received treatment continuously until disease progression or for a maximum of 18 months. Treatment was applied daily for an average of 18 h per day.

Patient evaluation. Objective tumor assessment was performed by Gd-enhanced MRI according to a strictly defined protocol. MRI scanning was performed at trial entry within one week of NovoTTF-100A treatment initiation and after every treatment course (28–30 days). All scans were reviewed by a board certified radiologist (J.V.). The assessment of tumor response was based on criteria defined by Macdonald *et al.* (32). Study visits were performed once per week during the first month of treatment and monthly thereafter. The following examinations were carried out at each visit: Neurological evaluation, EKG, complete blood count with differential, chemistry panel, and coagulation studies. Adverse events occurring during treatment or up to 60 days after termination of therapy were scored according to the common toxicity criteria scale (version 3). Disease progression was not captured as a serious adverse event.

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Disruption of Cancer Cell Replication by Alternating Electric Fields

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ABSTRACT

Low-intensity, intermediate-frequency (100–300 kHz), alternating electric fields, delivered by means of insulated electrodes, were found to have a profound inhibitory effect on the growth rate of a variety of human and rodent tumor cell lines (Panc1a C, U-118, U-87, H-1299, MDA231, PC3, B16F1, F-98, C-6, RG2, and CT-26) and malignant tumors in animals. This effect, shown to be nonthermal, selectively affects dividing cells while quiescent cells are left intact. These fields act in two modes: arrest of cell proliferation and destruction of cells while undergoing division. Both effects are demonstrated when such fields are applied for 24 h to cells undergoing mitosis that is oriented roughly along the field direction. The first mode of action is manifested by interference with the proper formation of the mitotic spindle, whereas the second results in rapid disintegration of the dividing cells. Both effects, which are frequency dependent, are consistent with the computed directional forces exerted by these specific fields on charges and dipoles within the dividing cells. *In vivo* treatment of tumors in C57BL/6 and BALB/c mice (B16F1 and CT-26 syngeneic tumor models, respectively), resulted in significant slowing of tumor growth and extensive destruction of tumor cells within 3–6 days. These findings demonstrate the potential applicability of the described electric fields as a novel therapeutic modality for malignant tumors.

INTRODUCTION

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarization (1). The transmission of such fields by radiation is insignificant, and therefore they are usually applied directly by contact electrodes, although some applications have also used insulated electrodes. Some well-known examples of such effects include nerve, muscle, and heart stimulation by alternating electric fields (1, 2). In addition, low-frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing (3). However, as the frequency of the electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions, although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper-depolarization cycles are integrated such that the net effect is nulled. At very high frequencies (i.e., above many MHz), although the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as frequency, field intensity, or tissue dissipation factor increases (4). This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radio frequency tumor ablation, which can be applied through insulated electrodes (5). Intermediate-frequency electric

fields (i.e., tens of kilohertz to megahertz) alternate too fast for causing nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields of low to moderate intensities are commonly considered to have no biological effect (4). However, a number of nonthermal effects of minor biological consequence have been reported even at low field intensities. These include microscopic particle alignment (i.e., the pearl chain effect; Ref. 6) and cell rotation (7, 8). With pulsed electric fields of 10³ V/cm and 100-ns pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation (9).

In the present study we show for the first time, to our knowledge, that very low-intensity (<2 V/cm), intermediate-frequency (100–300 kHz), alternating electric fields induced by insulated electrodes have specific inhibitory effects on dividing cells in culture. We demonstrate that applying these fields to cancerous cells leads to proliferation arrest and cell destruction. When applied to syngeneic mice tumor models, these tumor treating fields (TTFields) cause a significant reduction in tumor growth rate without any significant side effects.

MATERIALS AND METHODS

In Vitro Experimental Set Up. Cultures were grown in standard culture dishes (4-well) cell culture chambers; SN 138121; Nalge Nunc International). The TTFields were generated by pairs of 15-mm-long, completely insulated wires (P/N K-30-1000; VT Corporation; outer diameter, 0.5 mm; ethylene tetrathylfluoride insulation thickness, 0.125 mm; dielectric breakdown, 1800 V/mm) fixed to the bottom of each dish at a distance of 1 mm from each other. The wires were connected to an oscillator (GFG8219A; Instek) and a high-voltage amplifier (A303; A. A. Lab Systems Ltd.) that generated the required sine-wave signals (range, 300–800 V). Cells were plated by carefully spreading 10 µl of DMEM (Biological Industries Ltd., Beit Haemek, Israel) containing 1.5×10^4 cells along the gap between the wires (Fig. 1A). After the cells settled and attached to the plate surface, 500 µl of DMEM were added to each culture dish, which was then transferred to a 5% CO₂ humidified incubator held at 36°C. The culture was incubated for a control period of 24 h before treatment. Culture medium was replaced manually every 24 h throughout the experiments. TTFields were then applied by connecting the wires to a high-voltage amplifier operated by a signal generator with frequency and amplitude controls. Finite element simulation of the TTFields generated between the wires demonstrated that the field in the vicinity of the cell culture was homogenous (not shown). Eleven different types of cancerous cell lines were subjected to TTFields. These included human melanoma (Panc1a), glioma (U-118, U-87), Lung (H-1299), prostate (PC3), and breast (MDA231) cancerous cell lines as well as mouse melanoma (B16F1), rat glioma (F-98, C-6, and RG2), and mouse adenocarcinoma (CT-26) cell lines (all from American Type Culture Collection, except for Panc1a, which was a generous gift from Dr. Ruth Halaban, Department of Dermatology, Yale University School of Medicine). In addition, a noncancerous cell line (BFH) was grown under conditions that stunt cell replication (0.1% FCS) and then subjected to TTFields. Also, segments of excised rat mesentery and diaphragm were subjected to the fields *in vitro*. Colorimetric cell counts were made every 24 h after seeding using the standard 2,3-bis(2-methoxy-4-nitro-5-sulphophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide method to measure cell proliferation as described previously (10) using cell proliferation assay kit (Biological Industries, Beit Haemek, Israel). In brief, culture media was replaced with 0.2 ml of preheated 2,3-bis(2-methoxy-4-nitro-5-sulphophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide reagent and incubated for 1 h at 37°C in a 5% CO₂ incubator. After incubation and gentle stirring,

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0.15 ml of the reaction solution was transferred to a 96-well plate (SN 92696; TPP, Trasandigen, Switzerland). The absorbance of the samples was then read with a spectrophotometer (Tecan ELISA Reader; 450 nm). The colorimetric measurements at each time point were normalized to the measurement performed immediately before beginning of treatment. To verify that the colorimetric assessments were accurate, direct visual cell counts were performed on sample culture dishes. At the optic densities used (0.2–2), optic density was linearly related to the number of cells in the culture dishes ($n = 10$; $r^2 = 0.99$). The growth rate of both treated (GR_t) and control cultures (GR_c) was calculated for each experiment by plotting the optic density values on a logarithmic scale and fitting a linear regression line to the values. The growth rate for each culture dish was the slope of this linear regression. The therapeutic enhancement ratio (TER) was calculated as the ratio of the decrease in the growth rate of treated cells compared with the growth rate of control cells $[(GR_c - GR_t)/GR_c]$. Thus, if the increase in the number of treated cells is equal to that of the controls, $TER = 0$; if the increase in cell number is smaller in the treated cultures than in the controls, $TER > 0$; and if the number of cells in the treated cultures decreases absolutely, $TER > 1$.

In time-lapse microphotography experiments, cell lines were grown on a 35-mm standard culture dish (SN 430165; Corning Inc.) by plating 3×10^4 cells in 2.5 ml of DMEM with 25 mM HEPES. The Petri dish temperature was controlled at 34°C (B16F1) or at 37°C (all other cell lines). Subsequently, two parallel insulated wires were positioned on the bottom of the dish with 1 mm distance between them through which TTFields were applied. The entire set-up was placed on an inverted microscope (Eclipse TS-100; Nikon) and video microphotographs at $\times 200$ magnification were taken with a standard VCR camera (Handicam X 320; Sony). Photographs were captured using a personal computer every 60–120 s for 6–10 h/culture.

Fluorescent Labeling of α -Tubulin, Actin, and DNA. Mouse melanoma cells were grown on coverslips and subjected to TTFields for 24 h. After treatment, the medium was removed, and the cells were washed in a buffer solution [10 mM 4-morpholinethanesulfonic acid, 150 mM NaCl, 5 mM EGTA, 5 mM MgCl₂, and 5 mM glucose (pH 6.1)], permeabilized, and fixed with 0.5% Triton X-100 and 0.25% glutaraldehyde (Sigma) for 5 min and then post-fixed with 1% glutaraldehyde for 20 min. Subsequently, the cells were washed in PBS and 1 mM sodium borohydride (Sigma) to eliminate autofluorescence. The coverslips were then incubated with a primary antibody clone for α -tubulin (DM1A; Sigma) for 30 min, washed, and incubated for 30 min with a secondary antibody (Alexa Fluor 488 goat antimouse IgG; Molecular Probes). Rhodamine-conjugated phalloidin (Sigma) was added with the secondary antibody to stain actin filaments. The cells were then washed and incubated with 4',6-diamidino-2-phenylindole (Molecular Probes) to stain the DNA. After staining, the coverslips were mounted and viewed with a fluorescence microscope at $\times 630$ magnification and photographed.

Electric Field Measurement. The electric field intensity in the culture medium was measured by means of a probe, consisting of two (0.25 mm in diameter) insulated wires with exposed tips 0.5 mm apart, that was dipped in the culture medium. The wires were connected to a high-input impedance differential amplifier that translated the waveform amplitude into a calibrated steady voltage that was digitally recorded. Field intensities throughout the manuscript are expressed in peak voltage amplitude per centimeter (V/cm). Care was taken to eliminate any pickup from the field outside the culture medium. Continuous field monitoring could also be made by measuring the potential drop across a 100 Ω resistor placed in series with one of the field-generating wires. The voltage drop on this resistor was linearly correlated to the field intensity ($r^2 = 0.96$). To verify that the experimental setups were not exposed to any significant magnetic fields, the electromagnetic radiation in the immediate vicinity of the treated cultures was measured using a loop antenna (EMCO 6507 1 kHz to 30 MHz) connected to a spectrum analyzer (Anritsu 9 kHz to 2.2 GHz). The electromagnetic radiation in the 100–300-kHz range within the incubators containing treated culture dishes was found to be 10^{-12} Tesla and within animal cages containing TTField-treated mice, 10^{-16} Tesla, i.e., negligible.

Finite Element Simulations of Electric Field Distribution. The calculations of the electric field within the cells are based on finite element mesh (11), using a simplified description of the cell morphology (see Fig. 7). In all calculations, the dielectric constant of both the cytoplasm and medium was 80, their conductance was 0.3 S/cm, the cell diameter was 10 μ m, and the membrane thickness was 3 nm (with a dielectric constant of 3). The electric field

intensity was mapped within the cell, based on the amplitude (1 V/cm), frequency (100 kHz) and waveform (sine) of the electric field applied to the cell culture. The force exerted by an inhomogeneous field, such as that created inside the cells on a single tubulin dimer, was calculated based on the direct interaction between the electric field and the dipole. The force exerted on a microscopic polarizable organelle was calculated by the following equation (12):

$$\langle \vec{F} \rangle = 2\pi r^2 \epsilon_m \text{Re}[K(\omega)] \nabla E_{\text{RMS}}^2 \quad (1)$$

where $\langle \vec{F} \rangle$ is the expectation value of the force vector, Re symbolized the real component of the variable, ∇ is the divergence of the variable, ϵ_m is the cytoplasm dielectric constant, r is the tubulin dimer length or particle radius, E_{RMS} is the RMS value of the electric field, and $K(\omega)$ is the Clausius-Mossotti factor:

$$K(\omega) = \frac{\epsilon_p^* - \epsilon_m^*}{\epsilon_p^* + 2\epsilon_m^*} \quad (2)$$

$$\epsilon^* = \epsilon - j \frac{\sigma}{\omega}$$

where ϵ_p^* , ϵ_m^* are the complex dielectric constants of the particle and cytoplasm respectively, each of which is calculated from the dielectric constant (ϵ) and conductance (σ) as a function of frequency (ω). $K(\omega)$ in this case is always positive at the relatively low frequencies used (i.e., 100 kHz), assuming that at these frequencies, $\epsilon_p^* > \epsilon_m^*$. This means that the force acting on a polarizable particle will always act in the direction of the convergence of the electric field lines. The terminal velocity of particles due to these forces was calculated using Stoke's law.

In Vivo Experimental Setup. TTField treatment was applied by means of 10-mm-long pairs of parallel, insulated wires (outer diameter, 0.5 mm; insulation thickness, 0.125 mm; Tefzel) placed intradermally on the back of a mouse. Another pair of identical wires was placed parallel to the first pair in each mouse, with an interval of 5 mm between the pairs. Cell line inoculums were injected (4 μ l; 3×10^3 cells) intradermally in between the two members of each pair of implanted wires. Only one pair was then connected to a voltage amplifier to apply 100 kHz of TTFields treatment to one tumor. The other pair of wires was left disconnected, and the tumor between them served as a paired control of the treated tumor (see Fig. 1B). Tumors were measured using a caliper. Tumor size was calculated by multiplying maximal tumor length by maximal tumor width. Animal experiments were conducted in accordance with the Technion-Israel Institute of Technology guidelines for the care of laboratory animals.

RESULTS

Effect of TTFields on Cells in Culture. More than 500 culture dishes were exposed to TTFields. The number of cells in each treatment dish was assessed periodically using colorimetric determination (as described in "Materials and Methods"). Because under control conditions, most of the cell lines had doubling times of less than 24 h (range, 17–24 h; except for PC-3 for which the doubling time was 73 h), treatment duration was at least 24 h. Exposure began 24 h after seeding and was continued for up to 72 h. In all cell lines tested, 24-h exposure to TTFields at 100 kHz (at an intensity of 1.0–1.4 V/cm) caused significant inhibition of cell proliferation (TER range, 0.14–0.96; $P < 0.05$; Fig. 1C). This effect lasted beyond the exposure time of the cells to TTFields. In fact in some experiments (e.g., malignant melanoma), culture growth was stunted for as long as 72 h after TTField exposure was terminated (Fig. 2A).

We next checked whether nonreplicating cultures and tissues are affected by TTFields. BHK cultures were maintained in low-serum (0.1% FCS) conditions to slow their replication rate. These cultures were then exposed to 100 kHz of TTFields (at an intensity of 1.2 V/cm) for 24 h. No significant difference in cell number between control and TTField-treated cultures was observed under these con-

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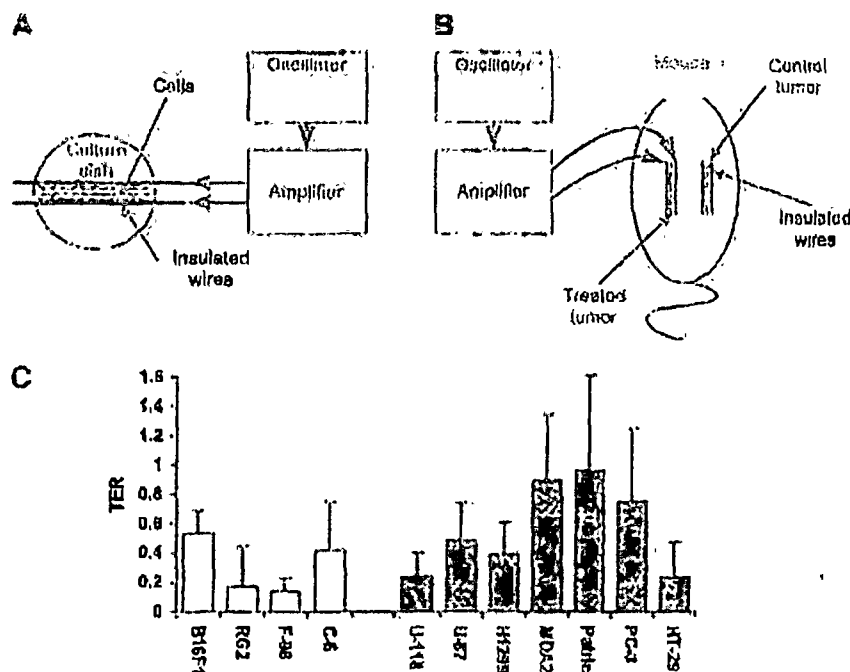


Fig. 1. Schematic representations of experimental setups for *in vitro* (A) and *in vivo* (B) are shown. C. TTFields inhibit the growth of cancerous cell lines *in vitro*. Cultures were exposed to 100 kHz TTFields at an intensity of 1–2.5 V/cm. Ordinate, TER, i.e., the ratio of the decrease in the growth rate of treated cells compared with the growth rate of control cells ($(OR_0 - OR)/OR_0$). In all four animal cell lines (C) and seven human cell lines (C) tested, the ratio is greater than 0, indicating an inhibition in the growth rate of the treated cultures compared with temperature matched controls. All effects were statistically significant ($P < 0.05$; Student's *t* test).

ditions ($P = 0.97$). After returning these cultures to normal media (10% FCS), normal replication resumed both in cultures exposed to TTFields and in control cultures. We also tested the effect of TTFields treatment on the number of viable cells in nonreplicating tissues dissected from rats. Four segments of rat mesentery and four segments of rat diaphragm were exposed to 100 kHz of TTFields at an intensity of 1.2 V/cm for 24 h. No differences were observed between the number of viable cells in both types of treated tissues compared with control tissues (mesentery, $P = 0.3$; diaphragm, $P = 0.54$).

To test the relationship between TTField intensity and inhibition of cell proliferation, mouse melanoma (B16F1) and rat glioma (F-98) cell lines were exposed to TTFields of different intensities between 1 and 2.5 V/cm. The inhibitory effect of TTFields on cell proliferation increased as intensity was raised (Fig. 2B) until complete proliferation arrest was achieved at intensities of 1.4 and 2.25 V/cm in melanoma and glioma cells, respectively.

The effects of TTFields are expected to be frequency dependent in view of the dependence of cell membrane electric impedance on frequency (due to the cell membrane capacitance). These changes in impedance render the fraction of field penetrating the cells a function of frequency. Therefore, we tested the frequency dependence of the inhibitory effect of TTFields on growth rate of cultured melanoma (B16F1) and glioma (F-98) cells. Comparison between the efficacy of the TTFields at different frequencies was performed by normalizing the TER to the electric field intensity. As seen in Fig. 2C, the inhibitory effect of TTFields was frequency dependent. Interestingly, the frequency at which maximal inhibition was achieved differed between cell types (120 kHz versus ~200 kHz for melanoma and glioma, respectively).

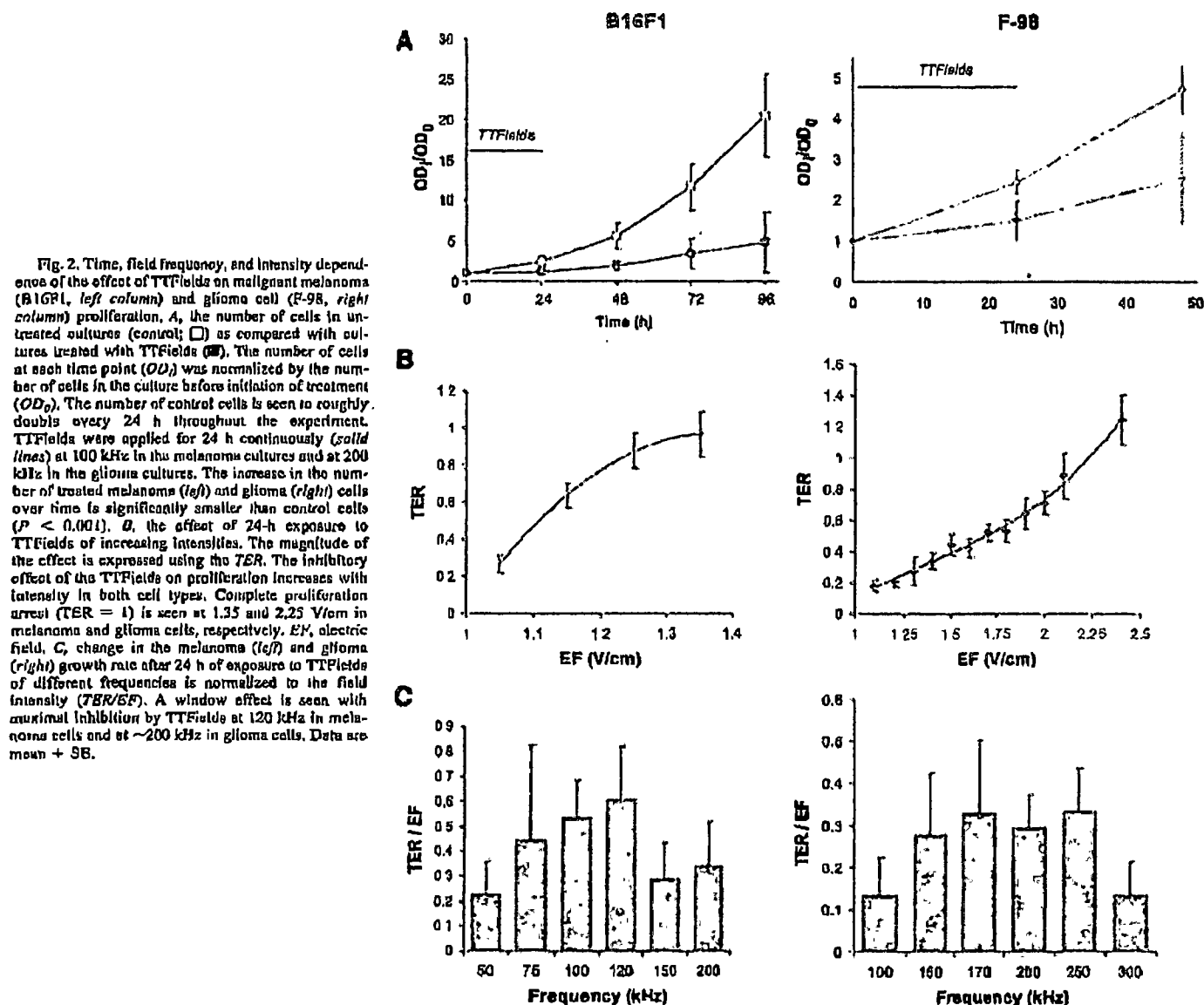
The Effects of TTFields on Cellular and Molecular Processes in Proliferating Cells. To gain insight into the cellular processes by means of which TTFields affect cell proliferation, time-lapse microphotography was performed while TTFields were applied to mouse melanoma cultures (see "Materials and Methods"). Several unique processes became evident in time-lapse microphotography of TTField-treated cultures. The most pronounced phenomenon was

prolongation of mitosis. In the treated cells, mitosis seemed to begin normally but was prolonged for variable periods of time before completing cleavage into two daughter cells. Fig. 3A shows an exemplary mitosis in a TTFields-treated cell. As seen in the treated cell, mitosis was not complete within 3 h. Due to this proliferation arrest, in treated cultures, mitosis lasted on average 124 ± 91 min (mean \pm SD, $n = 53$; range, 40–541 min), whereas under control conditions, average mitosis duration was 62 ± 8 min from cell rounding to cytokinesis (mean \pm SD, $n = 12$; range, 47–78 min). This prolongation is statistically significant ($P < 0.01$, Mann-Whitney *U* test).

The second major phenomenon, seen in the TTField-treated melanoma cultures, was that one-fourth of cells undergoing mitosis were destroyed as the formation of the cleavage furrow approached complete cell separation. During this process, the cell membrane ruptured, and many small membrane blebs formed, resembling post-mitotic apoptotic cell death (13). Two exemplary cells undergoing such destruction are shown in Fig. 3, B and C. Destructive effects were observed only in mitotic cells, whereas quiescent cells remained morphologically and functionally intact.

The third phenomenon, seen only in TTField-treated cultures, was nuclear rotation. In early mitosis, after cell rounding, nuclei could be seen rotating within the cell. A full rotation lasted on average 15 min. This effect resembles the whole-cell rotation previously described during exposure to intermediate-frequency alternating electric fields (7, 8).

A fundamental characteristic of electric fields is that at any point in space, they have a defined orientation corresponding to the direction of the force they exert on charges and polar elements. With regard to the latter, the force exerted by the field is maximal when the dipole is oriented in the direction of the field. With regard to the above, there are two main structural differences between quiescent and dividing cells. One is that the latter contain highly polar, spatially oriented microtubules and that they develop a directional, hourglass-shaped cell morphology during the cytokinesis phase. In view of these facts, one may expect that the electric field forces will have maximal effect



on the mitotic process when it is oriented along the lines of force of the field. To investigate this point, we fixed melanoma cell cultures and stained them with toluidine blue, immediately after 24 h of TTF treatment, to demonstrate mitoses and to distinguish vital from damaged or dead cells. The live and damaged mitotic cells (at the time of fixation) were grouped according to the orientation of their cleavage axis relative to the electric field direction. The cells were counted separately in each of four equal sectors that form angles of 0° , 45° (two sectors, 45 and 135), and 90° relative to the field direction. As seen in Fig. 4A, the live cells were randomly distributed in all sectors. In contrast, a much higher proportion of the damaged cells had their axis of division oriented along the field: 56% at 0° versus an average of 15% in each of the other orientations. Surprisingly, the number of cells per unit area in the two 45° sectors was found to be one-half that in the 0° sector. This finding may serve as an indication of an additional effect of TTFs: orientation of the cell division in the field direction. The cells in each of the above spatially oriented defined groups were further divided according to stages of mitosis at the time of fixation. At all stages, a higher fraction of damaged cells

had their axis of division oriented along the field. Moreover, 74% of the parallel oriented cells were damaged while being in metaphase (Fig. 4B).

The spatially organized mitotic spindle, which forms in dividing cells, consists of microtubules that have very large electric dipole moments (14) and may therefore be disoriented by the forces of the electric fields (15, 16). Actin filaments are also polar, however, they have no defined spatial orientation within the cells and are therefore not expected to be significantly affected by the fields. This prompted us to test whether TTFs disrupt mitosis by interfering with the normal formation, orientation, and movement of microtubules as compared with actin filaments as follows: Melanoma cell cultures were treated with TTFs for 24 h. After treatment, the cells were fixed, stained with monoclonal antibodies directed against microtubules and actin filaments, as well as for DNA, and thereafter studied with fluorescence microscopy (see "Materials and Methods"). In control cultures, 95% of cells undergoing mitosis exhibited the normal stages of mitosis with intact mitotic spindles. However, in TTF-treated cultures, more than one-half of the mitoses were abnormal.

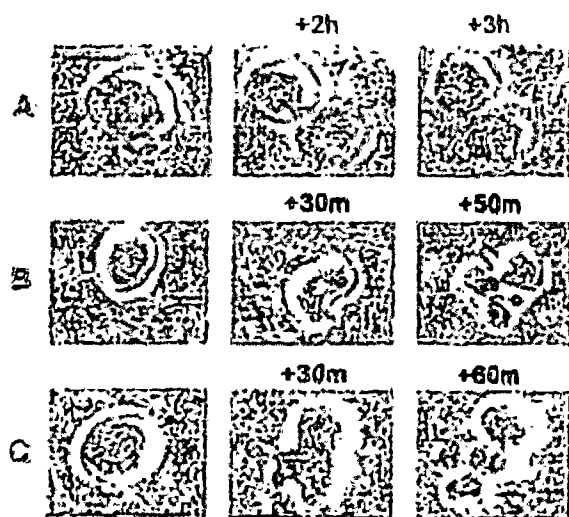


Fig. 3. Time-lapse microphotography of malignant melanoma cells exposed to TTFields. A, an example of a cell in mitosis arrested by TTFields. Contrary to normal mitosis, the duration of which is less than 1 h, the depicted cell is seen to be stationary at mid-cytokinesis for 3 h. B and C, two examples of disintegration of TTFields-treated cells during cytokinesis. Three consecutive stages are shown: cell rounding (left); formation of the cleavage furrow (middle); and cell disintegration (right). Scale bar = 10 μ m.

Fig. 5 shows examples of the different forms of abnormal mitosis seen under TTField treatment. These included polyploid cells in prophase, ill-separated, multi-spindled and single-spindled cells in metaphase, asymmetric anaphases, and a large proportion of cells in metaphase (>20%) with rosette shaped chromosome assemblies. The normal and abnormal stages of mitosis in control and TTField-treated cultures are summarized and compared in Fig. 5G. In general, these abnormalities may serve as an indication of interference of TTFields with the normal behavior of the microtubules. In contrast, staining for actin filaments showed no difference between TTField-treated and control cultures.

Effect of TTFields on Tumors *in Vivo*. To test whether TTFields are effective in destroying tumor cells *in vivo*, we tested their effect on two animal tumor models: C57BL/6 mice inoculated intradermally with malignant melanoma cells (B16F1) and BALB/c mice inoculated intradermally with adenocarcinoma cells (CT-26). TTFields were generated between implanted (intradermal) wholly insulated wires placed on both sides of the tumor (see Fig. 1B). Mice with implanted electrodes were treated for 3–6 days continuously beginning 1 day after cell line inoculation. We found that 100–200 kHz of TTFields at low intensities of <2 V/cm effectively inhibited malignant melanoma growth compared with the growth of nontreated control tumors. Photographs of examples of treated and nontreated malignant melanoma tumors are given in Fig. 6 for comparison. Treated tumors were significantly smaller than control tumors at the end of treatment (average treated tumor size was 47% of control tumor size; $n = 78$ mice, $P < 0.001$; Student's t test). Histopathological analysis of treated tumors showed extensive necrosis with aggregations of keratinocytic and karyolytic debris (Fig. 6F). To test whether TTFields are effective on different tumor types, BALB/c mice with intradermal adenocarcinomas were treated with the same field parameters. Photographs of examples of such a treated and a nontreated adenocarcinoma tumors are provided for comparison in Fig. 6B. The average effect of TTFields on adenocarcinoma carrying mice was less dramatic than that seen for malignant melanoma (average treated tumor size was 73% of control tumor size at the end of treatment; $n = 14$ mice). After treatment, the tumors and their adjacent tissues were fixated, stained with H&E, and analyzed histopathologically. No damage to the surrounding tissues was detected.

DISCUSSION

In this study, we have shown that when properly tuned, very low-intensity, intermediate-frequency electric fields (TTFields) stunt the growth of cancerous cells. We have demonstrated this inhibitory effect in all proliferating cell types tested, whereas, nonproliferating cells and tissues were unaffected. Interestingly, different types of cancerous cells showed specific intensity and frequency dependences of TTField inhibition. We have demonstrated that two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and cell destruction. The damage caused by TTFields to these replicating cells was shown to be dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is nonthermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors *in vivo*, showed no significant elevation in temperature compared with control cultures/mice. Also, TTFields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human cervical epithelial cells exposed to constant electric fields (17). At the subcellular level, we have found evidence indicating that TTFields disrupt the normal polymerization-depolymerization process of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to

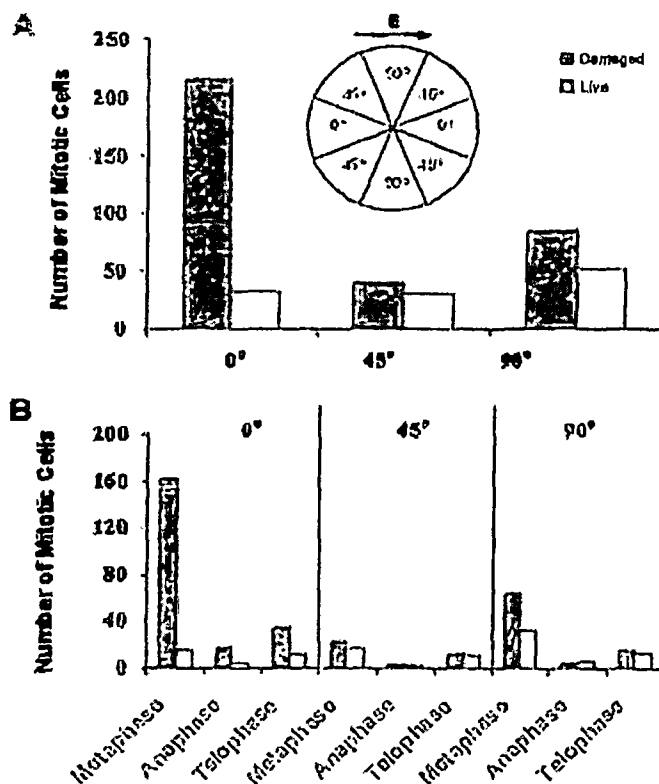


Fig. 5. Dependence of TTFields-induced cellular damage on the orientation axis of cell division relative to field direction. Outgoing represents the number of mitotic cells counted in four TTField-treated malignant melanoma cultures (100 kHz). A, total number of damaged (■) and live (□) mitotic cells in each of three sectors of different angles relative to the field direction (inset). The number of damaged cells is more than 5-fold larger than the corresponding number of live cells when division is aligned at or close to 0° relative to the electric field direction. In sectors of other angles, the number of damaged cells only slightly exceeds the live ones. Note that because the 45° area is double that of each of the other two sectors, the number of cells presented in this orientation was halved. B, dividing cell sensitivity to fields of different orientation at different stages of mitosis. When cell division axis is aligned at 0° to the electric field, the number of damaged cells (■) is significantly larger than that of live cells (□) at all three phases of mitosis. However, the highest number of damaged cells in this orientation is seen at metaphase (8-fold more than intact cells).

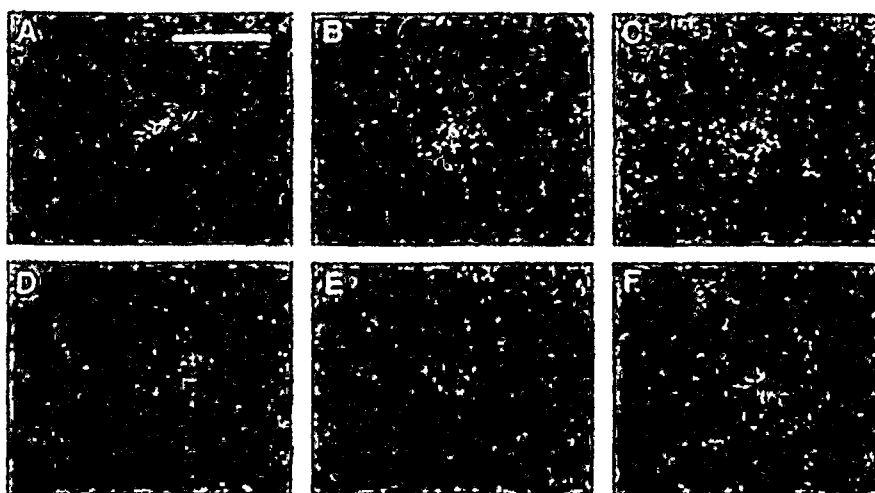
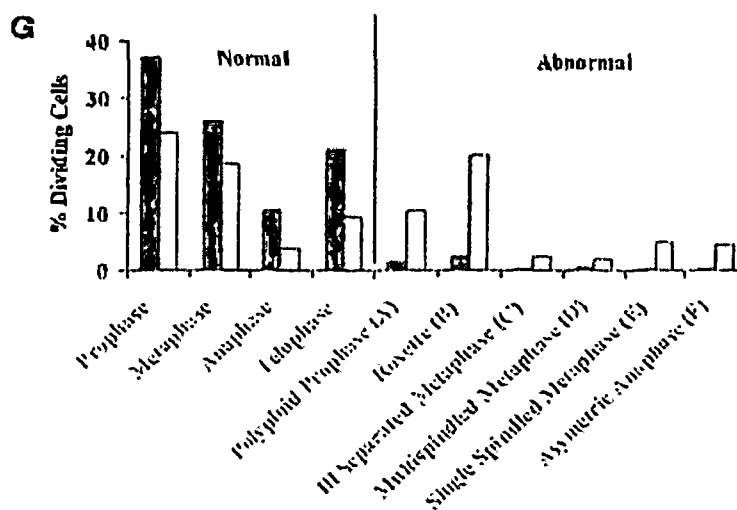


Fig. 5. Immunofluorescence staining of abnormal mitotic figures in TTFields-treated cultures. Malignant melanoma cultures ($n = 4$) were treated for 24 h at 100 kHz and then stained with monoclonal antibodies for microtubules (green), actin (red), and DNA (blue). The photomicrographs show exemplary abnormal mitoses including: polyloid prophase (A); coytic (B); III separated metaphase (C); multisplindled metaphase (D); single-splindled metaphase (E); and asymmetric anaphase (F). G, the percentage of treated (□) and control (■) mitotic cells in each of the normal and abnormal phases of mitosis.



TTFields are similar to the morphological abnormalities seen in cells treated with agents that interfere directly (18, 19) or indirectly (20–22) with microtubule polymerization (e.g., Taxol).

To explain how TTFields cause orientation-dependent damage to dividing cancerous cells and disrupt the proper formation of the mitotic spindle, we modeled the forces exerted by TTFields on intracellular charges and polar particles using finite element simulations (see “Materials and Methods”). We identified two main mechanisms by means of which the electric fields may affect dividing cells. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14 nm away from the growing end of a microtubule, to orient in the direction of the field (Fig. 7A). This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation (23). This effect can explain the mitotic arrest of TTField-treated cells (24). The second mechanism, which interferes with cell division and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in the simulations depicted in Fig. 7B, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. We see an

increased field line concentration (indicating increased field intensity) at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This inhomogeneity in field intensity exerts a unidirectional electric force on all intracellular charged and polar entities, pulling them toward the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1 μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5 pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization that is 4.3 pN (25). With regard to other particles such as cytoplasmic organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN resulting in their movement toward the furrow at velocities that may approach 0.03 $\mu\text{m/s}$. At such velocity, cytoplasmic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. We also found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTFields on the angle between division axis and the field (Fig. 4). In addition, the calculated dependence of the magnitude of this force on frequency (data not shown) is consistent with the experimentally determined frequency dependence of the

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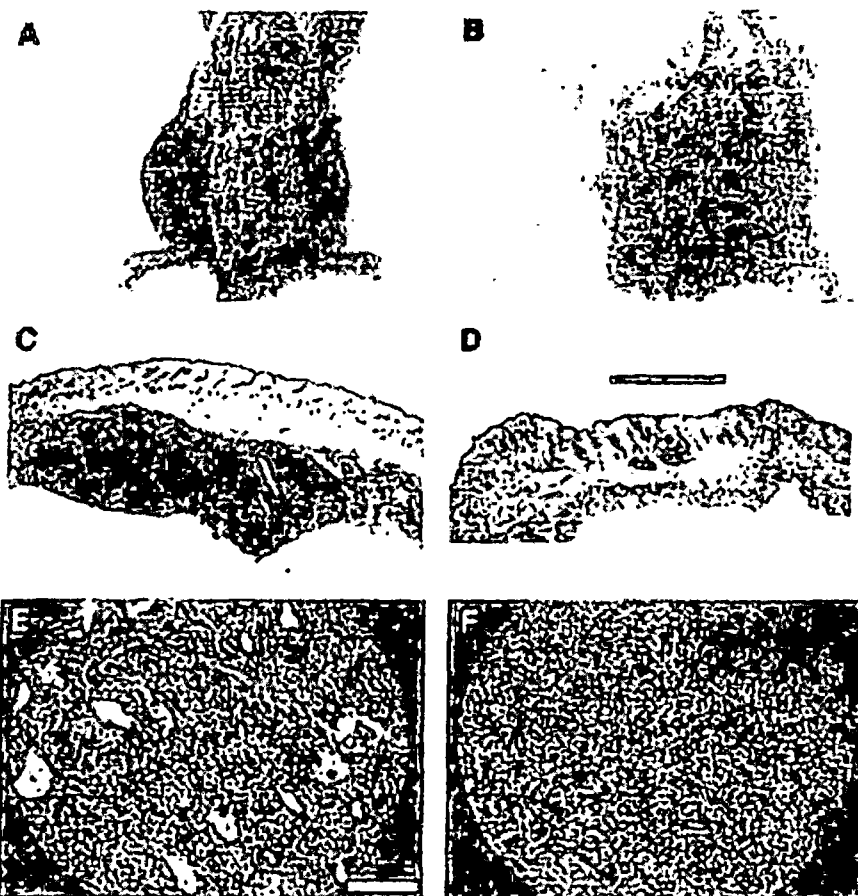


Fig. 5. *In vivo* effects of TTFields on intradermal tumors in mice. Malignant melanoma (A) and adenocarcinoma (B) tumor cells were injected in two parallel locations intradermally on the back of each mouse. Only the tumor on the left side of the mouse was treated. After 4 days of TTFields treatment (at 100 kHz), no tumor can be discerned on the treated side, whereas on the untreated side a large tumor has grown. C-F, histological sections of TTFields-treated intradermal melanoma versus a control (untreated) melanoma on the same mouse. C, after H&E staining, a large (5 mm diameter) nodule of melanoma cells can be seen in the dermis of the control tumor (X400). Note that due to the large size of the tumor, its deep portion has been lost in preparation. D, treated tumor; only two small (<0.4 mm diameter) nodules are present (scale bar = 0.5 mm). The nontumor structures of the dermis are morphologically intact. E, control tumor; malignant melanoma cells appear intact and viable (X200). (Scale bar = 100 μ m). F, only necrotic tissue and cellular debris are seen in the treated tumor.

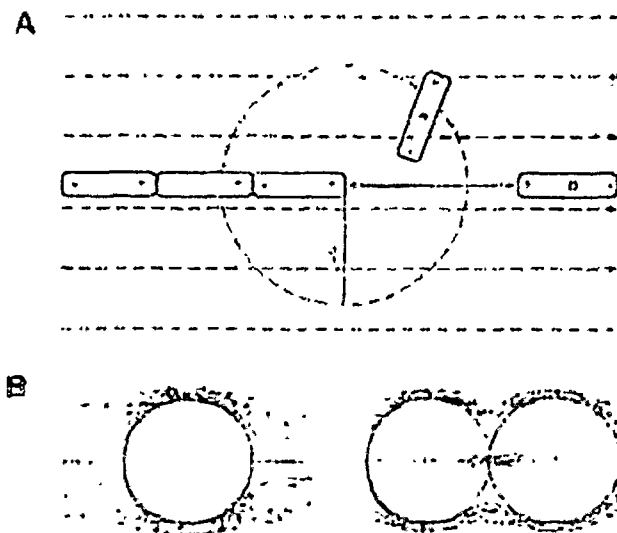


Fig. 7. A, schematic representation of two tubulin dimers positioned near the tip of an elongating microtubule in a dividing cell. The force that a 1-V/cm extracellular TTField exerts on a tubulin dimer located less than 14 nm away from the microtubule (a) is smaller than the force exerted by the polar microtubule tip, and therefore it will align according to the field generated by the microtubule. In contrast, dimers further than 14 nm from the end of the microtubule (b) are aligned by the force of the TTFields (dashed line) in a direction that may not be compatible with the polymerization depolymerization process. B, finite element mesh simulation of the lines of force of the electric field inside a quiescent cell (left) and a cell undergoing mitotic cytokinesis (right). The diameter of the cells in the simulations was 10 μ m and membrane thickness 5 nm. Inside the quiescent cell, the electric field is mostly uniform (equal distance between the lines of force). In contrast, in the dividing cell, the field is inhomogeneous—the field intensity (line density) increases toward the cleavage furrow.

Inhibitory effect of TTFields on melanoma and glioma cell proliferation (Fig. 2C).

In conclusion, we have demonstrated that TTFields inhibit both the proliferation of malignant cells in culture and the growth of tumors in mice while showing no general side effects or local histopathological damage. The mechanism of action of the fields is, at least in part, dependent on disruption of the microtubules of the mitotic spindle and the electric forces resulting from focusing of the field in the dividing cells. The highly specific effects of these fields on dividing cells, together with the relative ease of applying them, focusing them, and screening from them, make them an attractive candidate to serve as a novel treatment modality for cancer.

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RESEARCH ARTICLE Open Access

TTFields alone and in combination with chemotherapeutic agents effectively reduce the viability of MDR cell sub-lines that over-express ABC transporters

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Abstract

Background: Exposure of cancer cells to chemotherapeutic agents may result in reduced sensitivity to structurally unrelated agents, a phenomenon known as multidrug resistance, MDR. The purpose of this study is to investigate cell growth inhibition of wild type and the corresponding MDR cells by Tumor Treating Fields - TTFields, a new cancer treatment modality that is free of systemic toxicity. The TTFields were applied alone and in combination with paclitaxel and doxorubicin.

Methods: Three pairs of wild type/MDR cell lines, having resistivity resulting from over-expression of ABC transporters, were studied: a clonal derivative (C11) of parental Chinese hamster ovary AAB cells and their emetine-resistant sub-line Emr^h; human breast cancer cells MCF-7 and their mitoxantrone-resistant sub lines MCF-7/Mx and human breast cancer cells MDA-MB-231 and their doxorubicin resistant MDA-MB-231/Dox cells. TTFields were applied for 72 hours with and without the chemotherapeutic agents. The numbers of viable cells in the treated cultures and the untreated control groups were determined using the XTT assay. Student t-test was applied to assess the significance of the differences between results obtained for each of the three cell pairs.

Results: TTFields caused a similar reduction in the number of viable cells of wild type and MDR cells. Treatments by TTFields/drug combinations resulted in a similar increased reduction in cell survival of wild type and MDR cells. TTFields had no effect on intracellular doxorubicin accumulation in both wild type and MDR cells.

Conclusions: The results indicate that TTFields alone and in combination with paclitaxel and doxorubicin effectively reduce the viability of both wild type and MDR cell sub-lines and thus can potentially be used as an effective treatment of drug resistant tumors.

Background

Multidrug resistance (MDR) [1] is encountered when cancer cells are exposed to chemotherapeutic agents for a few replication cycles. It is manifested in reduced sensitivity to both the specific chemotherapy as well as to a number of structurally unrelated agents. This phenomenon obviously poses a serious impediment to successful chemotherapy. Three decades of multidrug resistance research have identified a number of mechanisms by

means of which cancer cells elude the effects of chemotherapeutic agents. The most often encountered MDR is the one resulting from over-expression of ATP-binding cassette transporters such as P-glycoprotein (MDR1), multidrug resistance-associated protein-1 (MRP1), and the breast cancer resistance protein (BCRP) [1-3]. These transporters, that recognize substrates of diverse chemical nature, lower the intracellular concentration of these substrates and are normally involved in detoxification [4,5].

MDR can potentially be overcome by the use of antitumor modalities that are not involved in membrane transport, for example, anti-angiogenic agents and physical

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modalities such as radiotherapy, heat and electric fields. Different types of electric fields were reported to inhibit cancer cell proliferation and cause cancer cell destruction, for example: exposure of cancer cells to low amplitude DC currents [6], low intensity, low frequency (50 Hz) AC currents [7] and the intermediate frequency (100-300 kHz) alternating electric fields, termed TTFs [8-12].

TTFs are a new physical cancer treatment modality that has recently been demonstrated to be highly effective when applied to cell cultures, animal cancer models, as well as patients suffering from locally advanced and/or metastatic solid tumors [8-12]. TTFs are alternating electric fields of low intensity (1-3 V/cm) and intermediate frequency (100 - 300 kHz) that are generated by special insulated electrodes applied to the skin surface. These specially tuned fields have no effect on quiescent cells while having an anti-proliferation and destructive effect on mitotic cells. This effect is due to the fact that during cytokinesis, TTFs exert forces that move charged or polar macromolecules and organelles towards the narrow neck, separating the newly forming daughter cells [8,9]. They also interfere with the polymerization processes of the microtubule spindle during cell division. Thus, TTFs disrupt the cell structure, inhibit cell division and result in cell death. In contrast to most anti-cancer agents, TTFs are not associated with any meaningful systemic toxicity [9-12]. Furthermore, it was recently shown that TTFs may be used clinically, not only as an anti-proliferation agent, but also as effective adjuvant to currently used chemotherapeutic agents [9].

In view of the above, the target of the present study was to test the possibility of using TTFs for treating multi-drug resistant cancerous and non cancerous cell lines, both as a standalone treatment and in combination with chemotherapy.

Methods

Materials

All cell culture media, serum and media supplements were obtained from Biological Industries, Beth Haemek, Israel. All drugs and chemical agents were obtained from Sigma.

Cell lines

The following cell lines and their drug resistant derivatives were used: A clonal derivative (C11) of parental Chinese hamster ovary AAB cells and their emetine-resistant sub-lines Emt^{R1} cells having ATP dependent MDR1 type drug resistance [13], a kind gift from Prof. G. Eytan Dept. of Biology, Technion, Haifa, Israel; Human breast cancer wild type MCF-7 cells, obtained from ATCC and their mitoxantrone-resistant sub-lines MCF-7/Mx having ABCG2 transporter [14], a kind gift from Prof. M. Lisco-

vitch, Dept. of Biological Regulation Weizmann Institute of Science, Rehovot, Israel; Human breast cancer wild type MDA-MB-231 cells obtained from ATCC and from which doxorubicin resistant MDA-MB-231/Dox cells were developed in our laboratory using a stepwise increase in drug concentration protocol. This procedure is identical with that developed for these cells in other laboratories [15] for inducing MDR1 type of ABC transporters. The AAB/Emt^{R1} cell lines were maintained as a monolayer in minimal essential medium containing 5% fetal calf serum, 2 mM glutamine, 100 units/ml penicillin G, and 100 µg/ml streptomycin sulphate. The Emt^{R1} cell medium also included 1 µM of emetine. The MCF-7/MCF-7MX and MDA-MB-231/MDA-MB-231Dox cell lines were maintained under monolayer conditions in DMEM containing 10% fetal calf serum, 2 mM glutamine, 100 units/ml penicillin G, and 100 µg/ml streptomycin sulphate. The MCF-7/Mx cell medium also included 250 nM of mitoxantrone and the MDA-MB-231/Dox cells medium also included 0.1 µM of doxorubicin.

All cells were kept in a 5% CO₂ incubator at 37°C. Exponentially growing cells were passaged twice a week using a standard trypsinization procedure.

Cytotoxicity assay

The level of resistance to doxorubicin and paclitaxel was determined by means of the XTT assay as previously described [8,9]. Briefly, 2×10^4 cells/well were plated in 24-well plate (NUNC), incubated without drugs for 24 h and then the initial number of cells, OD₀, was determined following incubation of with the XTT reagent using ELISA Reader (TECAN Sunrise, USA). The medium was then exchanged with ones containing different drug concentrations, 4 wells for each drug concentration (doxorubicin: 0.001-100 µM; paclitaxel: 0.0001-100 µM). After 72 h, the culture media was discharged, XTT reagent was added and the final cell number, OD_{72 h}, was determined. Data obtained from 3 - 5 experiments were collected and the mean values and standard deviations (SEM) of OD_{72 h}, representing final number of viable cells, were calculated for each drug concentration. Cell survival was presented as percentage of viable cells as compared to the corresponding viable cell number in no - drug controls. Drug concentrations inhibiting cell growth by 50% (IC₅₀) were calculated from relative survival curves using the median-effect principle [16].

Exposure to TTFs

As previously described [9,11], two pairs of electrodes, insulated by a ceramic having a very high dielectric constant (NovoCure Ltd, Haifa, Israel), were positioned at 90° with respect to each other in both treatment and control Petri dishes. The distance between the electrodes in each

pair was 20 mm. Each pair of electrodes was alternatively connected for 250 ms to a sinusoidal waveform generator (NovoTTF, NovoCure Ltd, Haifa, Israel) that produced 1.75 V/cm, 150 kHz fields in the medium [8]. The 150 kHz frequency of TTFs was found to be effective for treatment of all cells studied.

Four different sets of conditions in each experiment were conducted for each cell line in conjunction with each chemotherapeutic agent: untreated control cells, cells treated by the chemotherapeutic agent alone, cells exposed to TTFs, and cells having a combined TTFs - Chemo exposure (8 Petri dishes for each condition). After 72 h, the culture media was discharged, XTT reagent was added and the final number of viable cells, $OD_{72\text{ h}}$, was determined. Data obtained from 3 - 5 experiments were collected and the mean values and standard deviations (SEM) of $OD_{72\text{ h}}$ representing final viable cell numbers were calculated for each set of conditions. Cell survival was presented as percentage of viable cells out of the corresponding viable cell number in untreated controls. Student t-test was applied to assess the significance of the differences between results obtained for each of the four conditions tested. In order to assess the extent of possible chemotherapeutic dose reduction when applied in combination with TTFs, dose reduction indexes (DRI) for each TTFs/drug combination were calculated according to [17].

The DRI for the same level of effect (DRI_m) was calculated as the ratio of the concentration of drug alone to that of the combined drug-TTFs treatment:

$DRI_m = D_{m(\text{drug alone})}/D_{m(\text{combined treatment})}$. The DRIs determine the magnitude of dose reduction allowed for each drug when given in combination with TTFs, as compared with the agent dose that achieves the same level of effect. DRI values larger than 1 indicate increased sensitivity to the drug.

Intracellular Doxorubicin Accumulation

The intracellular accumulation of doxorubicin was determined for both wild type and drug resistant sub-lines. Cells were grown in total 16 Petri dishes (35 mm, NUNC) as monolayers for 24 h in drug-free medium and then incubated for 1 h in the absence or presence of doxorubicin with or without exposure to TTFs (1.75 V/cm, 150 kHz) (4 Petri dishes for each treatment condition). The cells were washed with ice cold PBS three times and solubilised with 100 μ l of 2% SDS. The solutions were then transferred to black 96-well plates (NUNC) and doxorubicin fluorescence was measured by spectrofluorometry (ELISA Reader TECAN F-200) at λ_{em} 600 nm and λ_{ex} 450 nm. Data obtained from 2 - 4 experiments were collected and the mean values and standard deviations (SEM) of doxorubicin fluorescence were calculated for each condi-

tion. Student t-test was applied to assess the significance of the differences between results obtained for each of the three cell pairs.

Results

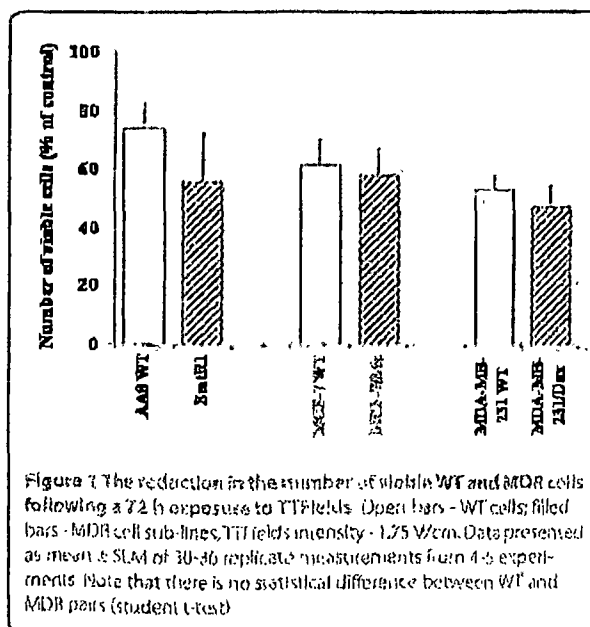
Effect of TTFs on wild type cells and their MDR sub-lines

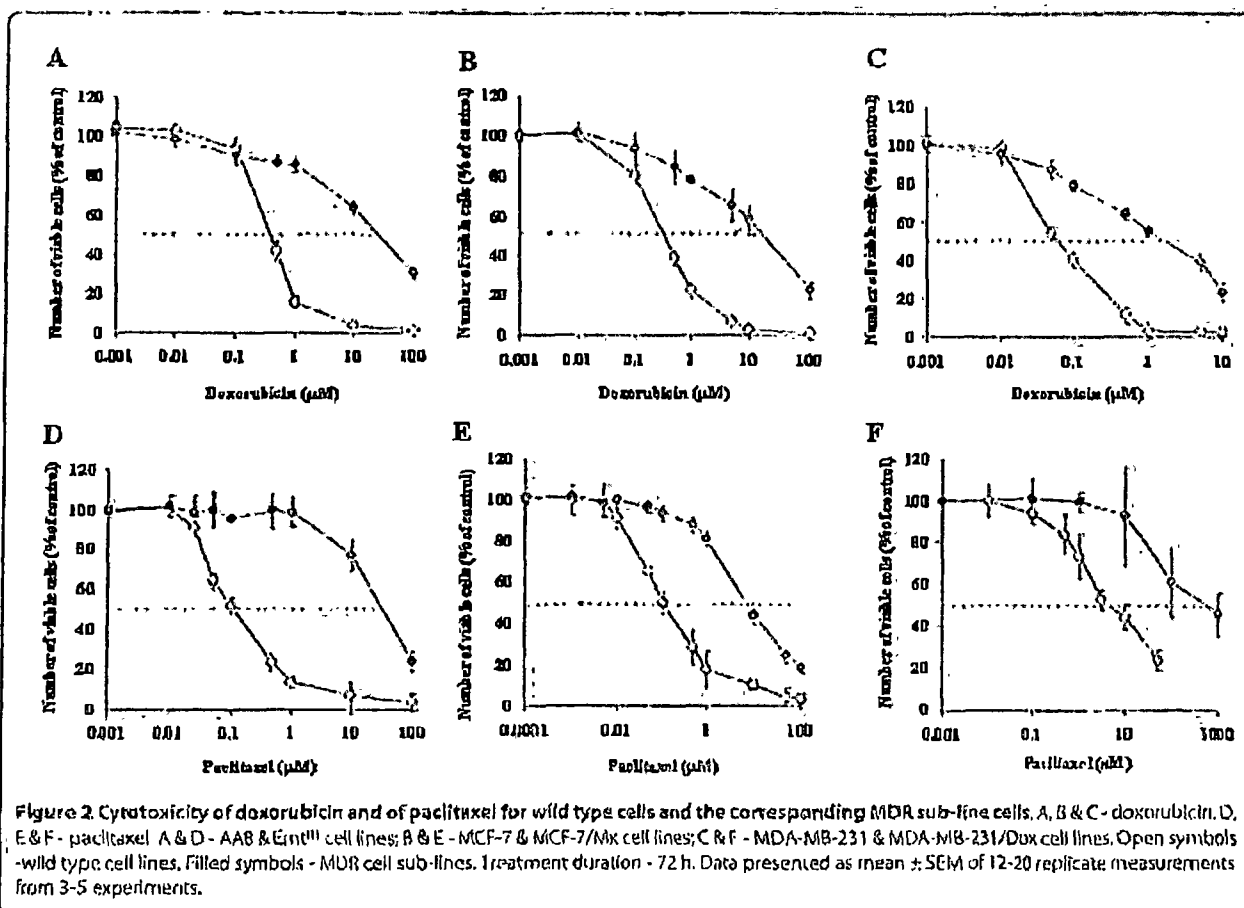
In order to study the TTFs effect, field intensities that reduce the WT cell survival by about 50% were used. A comparison between the survival of wild type and MDR cells, when exposed to such TTFs, is given in Figure 1. The reduction in the number of viable cells is seen to be very similar (48-61% of control) in all wild type and paired MDR lines. In other words, the drug resistant cell lines have about the same sensitivity to TTFs as their corresponding wild type cell lines.

Exposure to doxorubicin or paclitaxel in combination with TTFs

Figure 2 compares between the cytotoxicity-dose curves of chemotherapeutic agents (paclitaxel and doxorubicin) of wild type cells and MDR sub-lines. It is seen that the resistivity of the MDR sub-lines is manifested in a significant right shift of the drug cytotoxicity-dose curves. As a result of these shifts the calculated IC_{50} values (Table 1) for doxorubicin and paclitaxel, for all pairs of WT-MDR cell lines studied, give very high IC_{50} ratios (resistance index RI): 55 - 79 for doxorubicin and 128 - 653 for paclitaxel.

A comparison between cell viability following separate and combined TTFs/drug exposures are presented in Figure 3. It is seen that in all combined exposures cell survival is lower as compared with exposure to any of the





chemical agents (doxorubicin or paclitaxel) or TTFields alone (see Figure 1). Moreover, the cell survival of the MDR sub-lines and WT cell lines, when subjected to the combined exposure is similar, i.e. the resistivity or reduced drug sensitivity of MDR cells are not evident under these conditions.

Table 2 summarizes the combined treatment efficacy for MDR cells (see Figures 2 & 3) expressed in terms of Dose Reduction Index (DRI). TTFields are seen to increase the sensitivity to doxorubicin of all three MDR sub-lines by at least two orders of magnitude. The corre-

sponding increase for paclitaxel is even greater, i.e. two to three orders of magnitude. In other words, the efficacy of combined drug/TTFields treatment of MDR cells greatly exceeds that of treatment with drug alone.

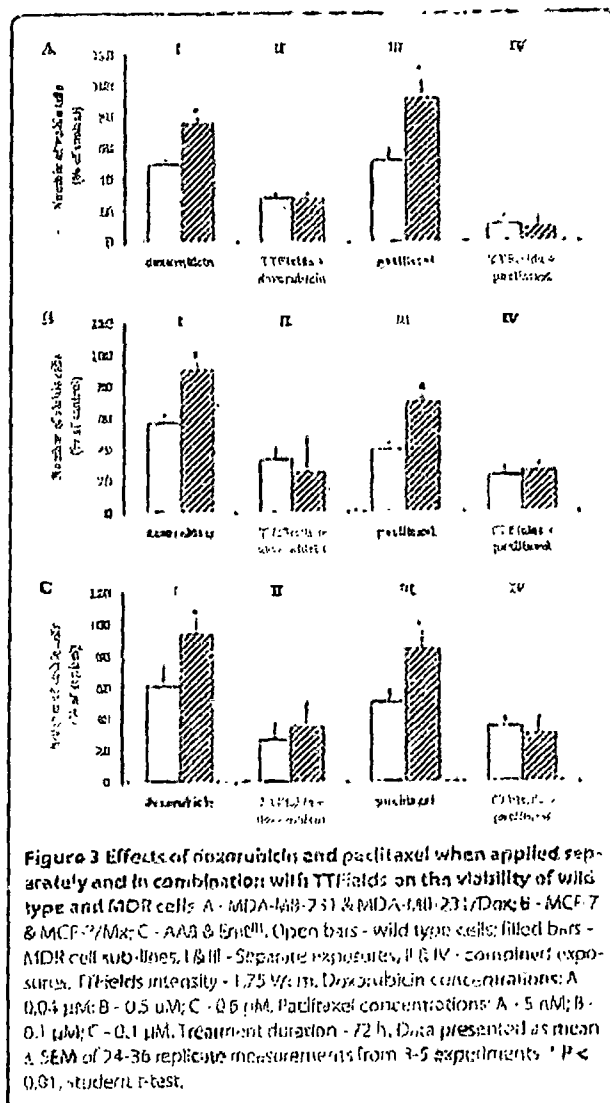
Intracellular Doxorubicin Accumulation

An inherent feature of overexpressed ABC transporters phenotype is the reduction in cell uptake of doxorubicin due to its exclusion [18]. The ability of MDR cells to exclude doxorubicin was determined by means of spectrofluorometric analysis. Figure 4A illustrates the intrac-

Table 1: IC₅₀ values for doxorubicin and paclitaxel

Drug	IC ₅₀					
	AAB	EmtR1	MCF-7	MCF-7/Mx	MDA-MB-231	MDA-MB-231/Dox
Doxorubicin (μM)	0.6	48.4	0.5	30.5	0.04	2.2
Paclitaxel (μM)	0.1	65.3	0.09	9.9	0.005	0.829

Drug concentrations inhibiting cell growth by 50% (IC₅₀) were calculated from relative survival curves (see Figure 2) using the median-effect principle [16].



cellular concentration of doxorubicin in AA8 (WT) and EmtR1 (MDR) cell lines as a function of extracellular doxorubicin concentration with and without exposure to TTFields. As the drug is partially excluded from drug resistant sub line, the relative intracellular doxorubicin concentration in EmtR1 cells is lower by 44.9, 49.7 and 49.8% at 15, 30 and 45 μ M extracellular doxorubicin concentration respectively, as compared with the wild type cells (Figure 4A, open symbols). Exposure of AA8 (WT) and EmtR1 (MDR) cell lines to TTFields during incubation with doxorubicin had no effect on the intracellular concentration of the drug in both wild type and drug resistant sub lines indicating that TTFields affect neither doxorubicin uptake nor its exclusion (Figure 4A, filled symbols). Figure 4B depicts doxorubicin accumulation by MDR sub lines relative to the corresponding WT cell

Table 2: Dose reduction indexes for MDR cell sub-lines treated alone and in combination with TTFields.

Drug	Dose reduction index (DRI)		
	EmtR1	MCF-7/Mx	MDA-MB-231/Dox
Doxorubicin	105	195	250
Paclitaxel	815	4404	> 10,000

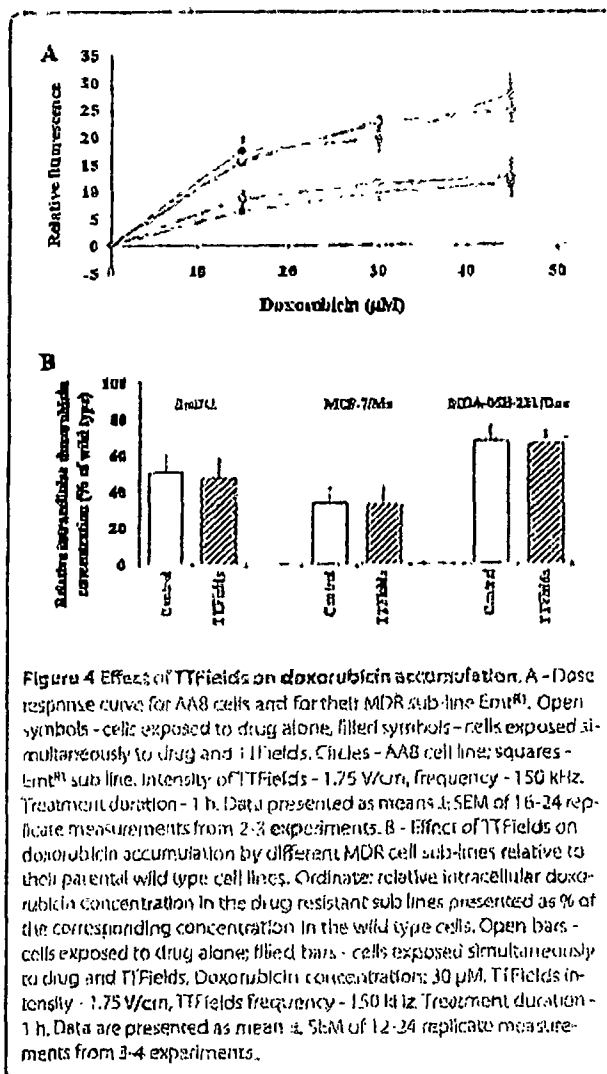
The DRI estimates the extent to which the dose of one or more agents in the combination can be reduced to achieve effect levels that are comparable with those achieved with single agents. The effect of TTFields/drug combined treatment for each MDR cell sub-line was as shown in Figure 3. The same effect of single drug was obtained from dose-response curves (see Figure 2). The DRI was calculated as a ratio of drug concentrations used alone vs. drug concentrations used in combination with TTFields.

lines exposed to 30 μ M of doxorubicin with and without TTFields. The relative intracellular doxorubicin concentration is lower by $49.7 \pm 5\%$ for EmtR1, $66.4 \pm 5\%$ for MCF-7/Mx and by $32.6 \pm 5\%$ for MDA-MB-231/Dox as compared with the corresponding wild type cells (Figure 4B, open bars). TTFields have no effect on intracellular doxorubicin concentrations in all wild type and drug resistant cell lines (Figure 4B, filled bars).

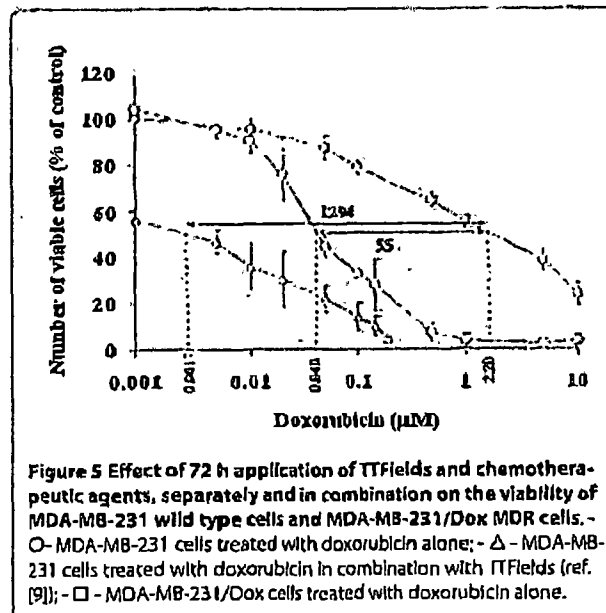
Discussion

ABC transporters provide vital protection from foreign compounds by exporting these compounds from the cell, thus lowering their intracellular concentration. Unfortunately, exposure of cancer cells to chemotherapeutics, mainly during relapse treatment, causes transporter upregulation such that the resulting over-expression of ABC transporters becomes one of the main causes of treatment failure. Moreover, various tumors such as renal cell, adrenocortical, colon and hepatocellular cancers express ABCB1 and are practically chemoresistant [19]. To overcome this problem chemosensitizers that block ABC transporter-mediated efflux were developed and have been used to combat MDR. However, this approach has not been clinically successful and therefore novel approaches that bypass, rather than block ABC transporters, are being sought for [20]. As the TTFields do not affect drug transport (see Figure 4) they fall into this category.

The results of this study clearly indicate that both the MDR and WT cells are similarly sensitive to TTFields. Moreover, TTFields were shown to enhance MDR cell sensitivity to chemotherapeutic agents, so as to equal that of WT cells under the same set of conditions (Figure 3). This phenomenon can only be partially explained on the basis of the corresponding dose - response curves (Figure 2) and the drug export rate (Figure 4). As demonstrated



In Figure 5, the dose - response curve of the drug resistant cells is shifted to the right relative to the WT cells (see also Figure 2). The magnitude of the shift is such that the 50% inhibition of WT cells that is obtained at a concentration of 0.04 μM requires a concentration of 2.2 μM for the MDR sub-line, i.e. a 55 fold higher concentration. However, the data depicted in Figure 4 and corresponding reports for low doxorubicin doses [21] indicate that the drug export lowers the intracellular concentration only by a factor of about 2. This means that some other factors must be responsible for the MDR resistance that corresponds to additional 20-30 fold drug concentration change. From the data in Figure 3A we also learn that both the MDR and WT cells are similarly highly sensitive to combined chemotherapy - TTFields treatments. Thus, while a 50% inhibition of MDR cells by doxorubicin alone requires a concentration of 2.2 μM , the combined treat-



ment of TTFields and low concentration of doxorubicin (0.0017 μM) is sufficient to induce a similar inhibition. This is equivalent to an increased intracellular concentration of doxorubicin by a factor of over 1000. Thus, TTFields seem to have effects specific to MDR cells, not related to drug transport, that increase the MDR cell's sensitivity to chemotherapy. This conclusion is consistent with that of others [22-24] that attribute the MDR resistance, in addition to reduced drug uptake, to a number of potential mechanisms such as: sugar metabolism and energy production, alterations in cytoskeletal elements, microtubule and mitochondria distribution, etc. Within the framework of the above suggested mechanisms [22-24] it seems that the integrity of cytoskeleton and microtubule as well as the mitochondria distribution may be the most vulnerable to the forces produced by TTFields. The former may be disrupted by particle movements induced by the dielectrophoresis induced during TTFields application [8] while the latter are highly polar in themselves and are therefore directly subjected to the alternating field forces.

Conclusions

The results of this study support the notion that TTFields may be used, both as an effective stand alone anti-proliferation agent for MDR cells, as well as an effective adjuvant that enhances chemotherapy efficacy. Furthermore, since TTFields are a physical modality, their therapeutic efficacy is independent of interaction with cell receptors. Therefore their efficacy is not expected to be limited to a specific set of cell types [8-12]. On the basis of the above, we believe that there is a high probability that TTFields

may prove to be an effective therapeutic modality to a wide range of human cancers including those that developed multi drug resistance.

List of abbreviations

MDR: multidrug resistance; TFields: tumor treating electric fields; DRI: dose reduction index; WT: wild type.

Competing interests

RS, ES and EK are employees of NovoCure Ltd. YP has a minority holding in NovoCure Ltd.

Authors' contributions

YP: Conceived the concept of TFields, designed experiments was involved in data analysis & interpretation of results and wrote the majority of the manuscript. RS: Participated in experimental design, supervised the experiment execution, analyzed results and wrote parts of the manuscript. ES: Carried out the experiments. EK: Participated in experimental design and in the interpretation of the results.

All authors read and approved the final manuscript.

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Research article

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Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields)

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Abstract

Background: The present study explores the efficacy and toxicity of combining a new, non-toxic, cancer treatment modality, termed Tumor Treating Fields (TTFields), with chemotherapeutic treatment in-vitro, in-vivo and in a pilot clinical trial.

Methods: Cell proliferation in culture was studied in human breast carcinoma (MDA-MB-231) and human glioma (U-118) cell lines, exposed to TTFields, paclitaxel, doxorubicin, cyclophosphamide and dacarbazine (DTIC) separately and in combinations. In addition, we studied the effects of combining chemotherapy with TTFields in an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients.

Results: The efficacy of TTFields-chemotherapy combination in-vitro was found to be additive with a tendency towards synergism for all drugs and cell lines tested (combination index ≤ 1). The sensitivity to chemotherapeutic treatment was increased by 1–3 orders of magnitude by adjuvant TTFields therapy (dose reduction indexes 23 – 1316). Similar findings were seen in an animal tumor model. Finally, 20 GBM patients were treated with TTFields for a median duration of 1 year. No TTFields related systemic toxicity was observed in any of these patients, nor was an increase in Temozolomide toxicity seen in patients receiving combined treatment. In newly diagnosed GBM patients, combining TTFields with Temozolomide treatment led to a progression free survival of 155 weeks and overall survival of 39+ months.

Conclusion: These results indicate that combining chemotherapeutic cancer treatment with TTFields may increase chemotherapeutic efficacy and sensitivity without increasing treatment related toxicity.

Background

A new physical cancer treatment modality termed Tumor Treating Fields, or TTFields, has recently been demonstrated to be highly effective when applied to cell cultures, animal cancer models, as well as to patients suffering from locally advanced and/or metastatic solid tumors [1-3]. In a pilot clinical trial, the medians of time to disease progression and overall survival of recurrent GBM patients treated by TTFields alone were more than double the reported medians of historical control patients [1]. In contrast to the widely used physical treatment modality, ionizing radiation, TTFields are not associated with significant side effects.

TTFields are low intensity (1-2 V/cm), intermediate frequency (100 - 200 kHz) alternating electric fields generated by special insulated electrodes applied to the skin surface. These specially tuned fields have no effect on quiescent cells while having an anti-mitotic effect on dividing cells. During cytokinesis, TTFields generate non-uniform intracellular fields that exert forces that move polar macromolecules and organelles towards the narrow neck, separating the newly forming daughter cells, by a process termed dielectrophoresis. These molecular and organelle movements, together with an interference with the spindle tubulin polymerization process, inhibit cell division and lead to cell death [2]. Fortunately, the dividing cells of the hematopoietic system are not affected by TTFields as the muscles surrounding the marrow containing bones serve as an effective electric field shield. Moreover, due to their relatively high frequency range and very low intensity, TTFields do not stimulate nerves and muscles, do not generate meaningful temperature elevation or puncture the cell membrane (as the strong electroporation fields do [4]). Thus, TTFields are not associated with meaningful toxicity in contrast to most anti-cancer agents currently in use [5].

In view of the unfavorable therapeutic indexes of the available effective chemical and physical (i.e. ionizing radiation) therapeutic agents, many cancer treatment protocols require simultaneous or sequential use of a number of therapeutic agents in an attempt to increase efficacy while maintaining tolerable toxicity [5-7]. Within this framework it is generally accepted that by adding ionizing radiation [8] to chemotherapy one gets both the benefit of the radiation effect as well as sensitization leading to an increased efficacy without a corresponding increase in toxicity. On the basis of the above this study explores the potential use of the new physical treatment modality, TTFields, in combination with chemotherapeutic agents in cell cultures, an animal tumor model, as well as in patients with glioblastoma (GBM). As TTFields are not associated with systemic toxicity [1] the expectation is that their addition will result in an increase in efficacy alone.

Methods

Cell cultures

Cells were cultured and maintained as previously described [1,2]. In brief: Human breast cancer (MDA-MB-231) and human glioma (U-118) obtained from ATCC (USA) were cultured in DMEM + 10% FCS media in a 5% CO₂ incubator at 37°C. Drops consisting of 200 µl suspension of cells (100 × 10³ cells/ml) were placed at the centre of 35 mm Petri dishes, incubated for 2 hours to allow for cell attachment, then 1.5 ml of media were added and incubation was continued for an additional 22 h. Following this, the baseline cell count was estimated using the XTT colorimetric method (expressed as OD₀). The media in the Petri dishes was replaced by fresh media (3 ml), with or without a chemotherapeutic agent and incubated at a final temperature of 37° ± 0.5°C for 24 to 72 hours after which the cell number was re-estimated (OD₁). The relative number of viable cells at each time point following baseline was expressed as OD₁/OD₀ and treatment efficacy as the % change in proliferation relative to control:

$$(OD_1/OD_0)_{\text{experiment}} \cdot 100 / (OD_1/OD_0)_{\text{control}} \quad (1)$$

TTFields treatment of cultures

As previously described [1,2], two pairs of electrodes, insulated by a high dielectric constant ceramic, were positioned normal to each other at a distance of 20 mm in treatment and control dishes. In the former, the electrodes were connected to sinusoidal waveform generator that generated fields of optimal frequencies in the medium [1,2,9]: 150 kHz for breast cancer and 200 kHz for glioma, that changed direction by 90° every 250 ms. Field intensity was measured as described previously [2] and expressed as V/cm. For 72 h experiments the TTFields intensity of 1.75 V/cm was used. For 24 h experiments 0.65, 1.25 and 1.75 V/cm TTFields were used.

Four different sets of experiments were conducted in conjunction with each chemotherapeutic agent: untreated sham control, treatment with TTFields, treatment with the chemotherapeutic agents, and combined TTFields - Chemo treatment.

Assessment of combination Index and dose reduction index

The Chou and Talalay [10] method for assessing the combined effect of multiple drugs was used for the drug - TTFields combinations. In order to assess whether the interactions between TTFields and each of the chemotherapeutic agents is synergistic, additive or antagonistic, combination indexes were calculated as follows; TTFields intensity replaced the concentration (dose) variable in the analyses. Dose-response curves were generated for TTFields and each drug to determine the median effect

points. Variable ratios of drug concentrations to TTFields intensities were used to calculate the Combination Indexes (CI) as follows:

$$CI = (C_{Drug(incombination), X\% effect} / C_{Drug(alone), X\% effect}) + (I_{TTFields(incombination), X\% effect} / I_{TTFields(alone), X\% effect}) \quad (2)$$

Where: C are the drug concentrations and I the TTFields intensities use to achieve a preset X% effect. Relationships of $CI < 1$ indicate more than additive – synergy, $CI = 1$ reflects additivity – summation and $CI > 1$ indicates less than additive or antagonism.

In order to assess whether TTFields increase the sensitivity of tumor cells to various chemotherapeutic agents, the dose reduction index (DRI) of for each of these agents was calculated according to [11]. In short, the median-effect plots were for each chemotherapy-TTFields combination, were constructed. The ratio of affected to unaffected number of cells (f_a/f_u) was plotted versus drug concentration on a log-log scale. The median effect point (D_m) was assessed by deriving the slope of the linear regression for each of the plots. The DRI for a 50% effect (DRI_m) was calculated as the ratio of D_m for drug alone and for combined drug-TTFields:

$$DRI_m = D_{m(drug alone)} / D_{m(combined treatment)} \quad (3)$$

A DRI greater than 1 indicates an increase in sensitivity to the drug. The greater the DRI, the more significant the possible dose reduction.

In-vivo experiments

Combined TTFields and Paclitaxel efficacy study in VX2 tumor bearing rabbits was conducted after approval by the NovoCure Internal Animal Care and Use Committee. All painful or anxiogenic procedures were performed under general anesthesia induced by intramuscular administration of 30 mg/kg of ketamine hydrochloride, 10 mg/kg xylazine hydrochloride and 1.5 mg/kg Acepromazine. The tumor tissue required for implantation was obtained from VX-2 tumor bearing carrier rabbits. The carrier rabbits had VX-2 tumors implanted intramuscularly in the thigh. When the tumor reached approximately 1 cm in diameter (about 3 weeks from implantation), the tumor was excised, minced in sterile saline and VX-2 tumor fragments obtained. Two fragments were injected using a large bore needle into the thigh, muscles of both legs in a recipient rabbit for tumor propagation. For experimental animals, after laparotomy, a fragment of tumor tissue (1 mm³) was implanted beneath the kidney capsule of the recipient rabbit.

The current experiment comprised 28 animals (7 in each of 4 groups). Fourteen days after tumor implantation the

initial tumor volume was assessed based on serial (2.2 mm interval) T1 weighted axial MRI images (1.5 Tesla, GE Genesis-Signa) obtained 3 minutes following IV injection of 3 ml of Gadolinium. Tumor volume was assessed from the area of the contrast enhancing lesion in each section. The animals were assigned randomly into 4 groups before treatment start:

1. TTFields treated group: TTFields were applied by using the NovoTTF-100A device (NovoCure LTD., Haifa, Israel). An optimal frequency of 150 kHz and intensity of 1–2 V/cm were used. TTFields were switched sequentially between two perpendicular field directions.

2. Control group: sham electrode heated to mimic heat generated by the TTFields treatment. (38–39.9 °C)

3. Paclitaxel (Medixel Injection., Taro Pharmaceutical Industries LTD., Israel) treated group: 5 mg/animal diluted in 100 ml of normal saline were infused intravenously over a period of 30 minutes. Premedication was given subcutaneous 8 hours before and immediately prior to Paclitaxel administration (Dexamethasone (Dexaveto-0.2 veterinary, V.M.D n.v/s.a Belgium) 0.5 mg/animal; Pramirine (Metoclopramide HCL, Rafa Laboratories LTD., Israel) 1 mg/animal; Diphenhydramine (10%, Medical M., Israel) 10 mg/animal).

4. Combined TTFields and Paclitaxel treatment as above.

TTFields were delivered to awake and behaving rabbits through four insulated electrode arrays placed circumferentially around the animal's abdomen, caudal to the ribcage. The electrode insulation consisted of a high dielectric constant (>10,000) ceramic (PMN-PT) allowing efficient energy transfer through the insulation into the animals body at the given frequencies. The electrodes were connected by a spiral cable to a swivel mechanism at the top of the cage, enabling the free movement. TTFields were generated using the NovoTTF-100A system (NovoCure Ltd., Haifa, Israel). The animals were treated for 21 days continuously with MRI performed on days 14 and 21 for tumor volume assessment. The TTFields intensity within the kidneys of the rabbits, using this electrode configuration, is between 1–3 V/cm (based on both finite element mesh simulations and direct measurements using an invasive probe – data not shown).

Pilot clinical trial

A single arm, pilot trial of the safety and efficacy of TTFields treatment was performed in 20 patients with histologically proven glioblastoma multiforme (GBM) that met the inclusion/exclusion criteria specified in Supplemental Material Appendix A (briefly, KPS 70–100%, Age ≥ 18). The trial was performed according to a protocol

approved by the Na Homolce Institutional Review Board and the Czech Republic Ministry of Health. The patients were divided into two groups: The first group included 10 patients with recurrent GBM treated with TTFields alone following failure of maintenance Temozolomide [1]. The second group consisted of 10 newly diagnosed patients who were at least 4 weeks post radiation therapy, who received TTFields combined with maintenance Temozolomide. Prior to initiation of treatment, all patients underwent a baseline contrast MRI of the head, chest radiograph, EEG, ECG, complete blood & urine analyses, physical examination and neurological status. The patients were hospitalized for 1–3 days for observation and then released home where they received multiple 4-week courses of continuous NovoTTF-100A treatment until progression. The patients were seen once/month at an outpatient clinic where they underwent an examination similar to the initial one. TTFields were applied to the patients using the NovoTTF-100A device set to deliver 200 kHz, 0.7 V/cm (RMS) fields (at the center of the brain) in 2 perpendicular directions, 1 second in each direction sequentially. The TTFields were applied continuously using four insulated electrode arrays, each having a surface area of 22.5 cm², placed on opposing sides of the head with the tumor positioned directly between the electrode pairs [1]. As previously reported, to avoid electrolysis at the electrode surface and intracellular ion concentration changes that accompany long term current application, the electrodes were completely insulated by a ceramic having a very high dielectric constant (>10,000) that allowed the generation of the necessary electric fields [1,2]. Using this electrode configuration, the lowest TTFields intensity at the center of the brain was 0.7 V/cm (RMS). This intensity was calculated using finite element mesh simulations and verified by direct measurement in large animals and a human volunteer [1].

The outcome endpoints of the study included safety, overall survival (OS) and progression free survival (PFS). Assessment of tumor response was based on monthly MRIs according to the Macdonald criteria [12]. Median OS and PFS were determined using Kaplan Meier curves [13]. In the first group, PFS in NovoTTF-100A treated patients was compared to a matched group of concurrent control patients who received salvage chemotherapy at recurrence (n = 18). PFS in Temozolomide/NovoTTF-100A treated patients was compared to the PFS of a

matched group of concurrent control patients (n = 32) who received Temozolomide alone (according to the protocol described by Stupp et al. [14]). OS in both groups was compared to matched historical control data with the same Karnofsky performance score (>60) and age [14].

Results

Breast cancer cell cultures

Dose – response of culture exposure to TTFields, paclitaxel, doxorubicin and cyclophosphamide, alone and in combination

The relationship between TTFields intensity, at 150 kHz, and cell proliferation rate is given in Figure 1A. At the lowest field intensity of 0.63 V/cm there is no significant change in cell proliferation. For TTFields intensities of 1.25, 1.75 and 2.95 V/cm cell proliferation decreases (control = 100%) to: $90 \pm 3\%$, $74 \pm 4\%$ and $25 \pm 5\%$, respectively. The dose-response curves of cells exposed to paclitaxel, doxorubicin and cyclophosphamide, alone and in combination with 1.75 V/cm TTFields for 72 hours, are given in Figures 1B, C & D. For each drug alone there is a decrease in cell proliferation with increase in concentration. For cyclophosphamide and doxorubicin complete inhibition of proliferation is achieved at high drug concentrations. For paclitaxel, the inhibitory effect of the drug saturates at about 300 nM, near the 13% level, indicating that a fraction of the cells are insensitive to the agent. Combined treatment with TTFields and each of the chemotherapeutic agents caused a leftward shift of the dose response curves. This shift can be expressed as a decrease in the drug concentration leading to 50% inhibition of cell proliferation (IC₅₀ – Table 1).

Time course of the effects TTFields, paclitaxel, doxorubicin and cyclophosphamide

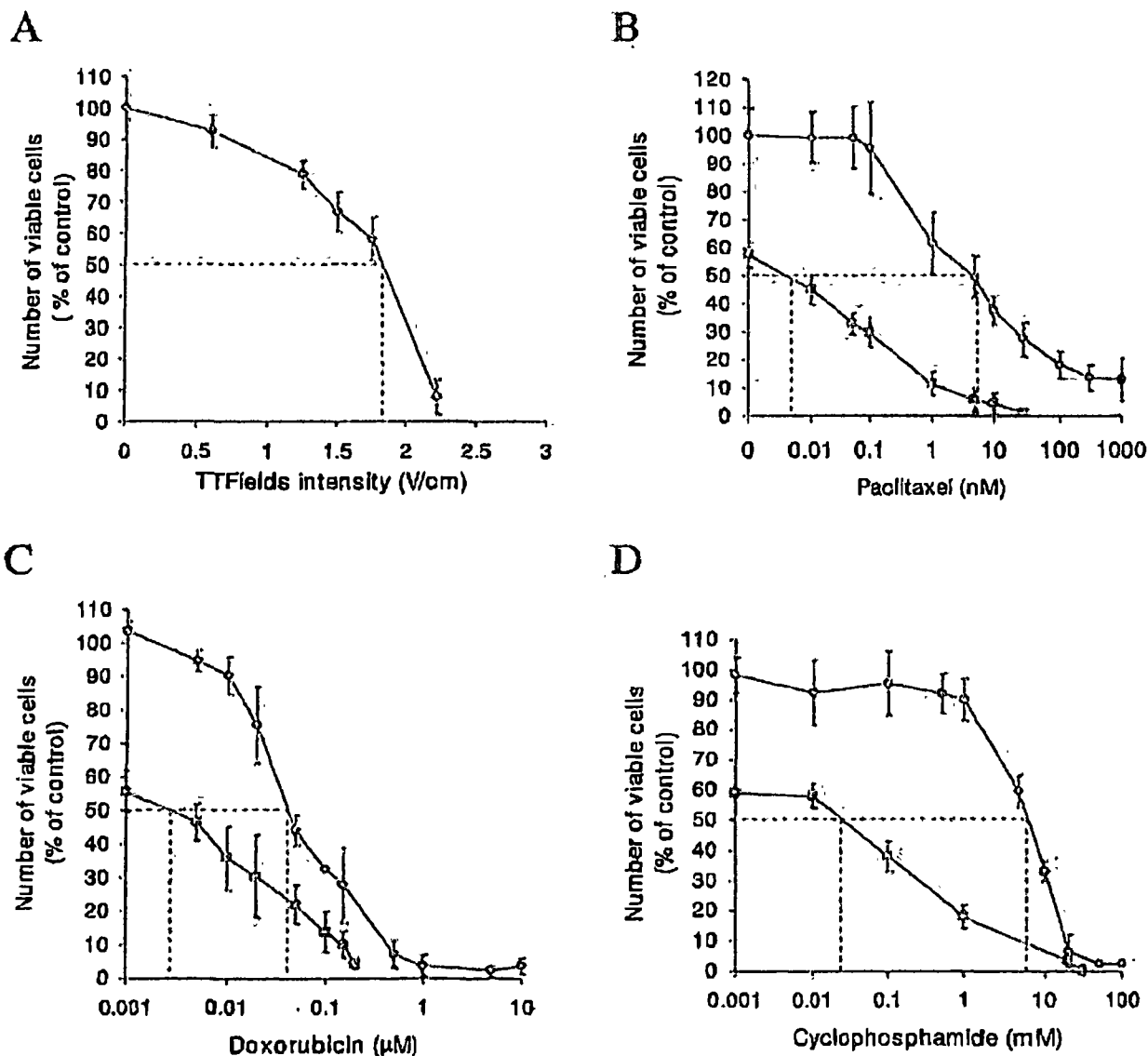
Figure 2 displays the time course of proliferation inhibition during a continuous 72 hour exposure to TTFields, paclitaxel, doxorubicin and cyclophosphamide alone and in combination with 1.75 V/cm TTFields. It is seen that in all cases the inhibition during combined exposure is greater than for the chemotherapeutic agent alone. The differences between the separate and combined effects increase with time.

Recovery from treatment

Figure 3 demonstrates that a 24 hour exposure to individual chemotherapeutic agents induces a reduction of approximately 25% in viable cell number compared to

Table 1: IC₅₀ for chemotherapeutic drugs alone and in combination with 1.75 V/cm TTFields after 72 hours of continuous treatment.

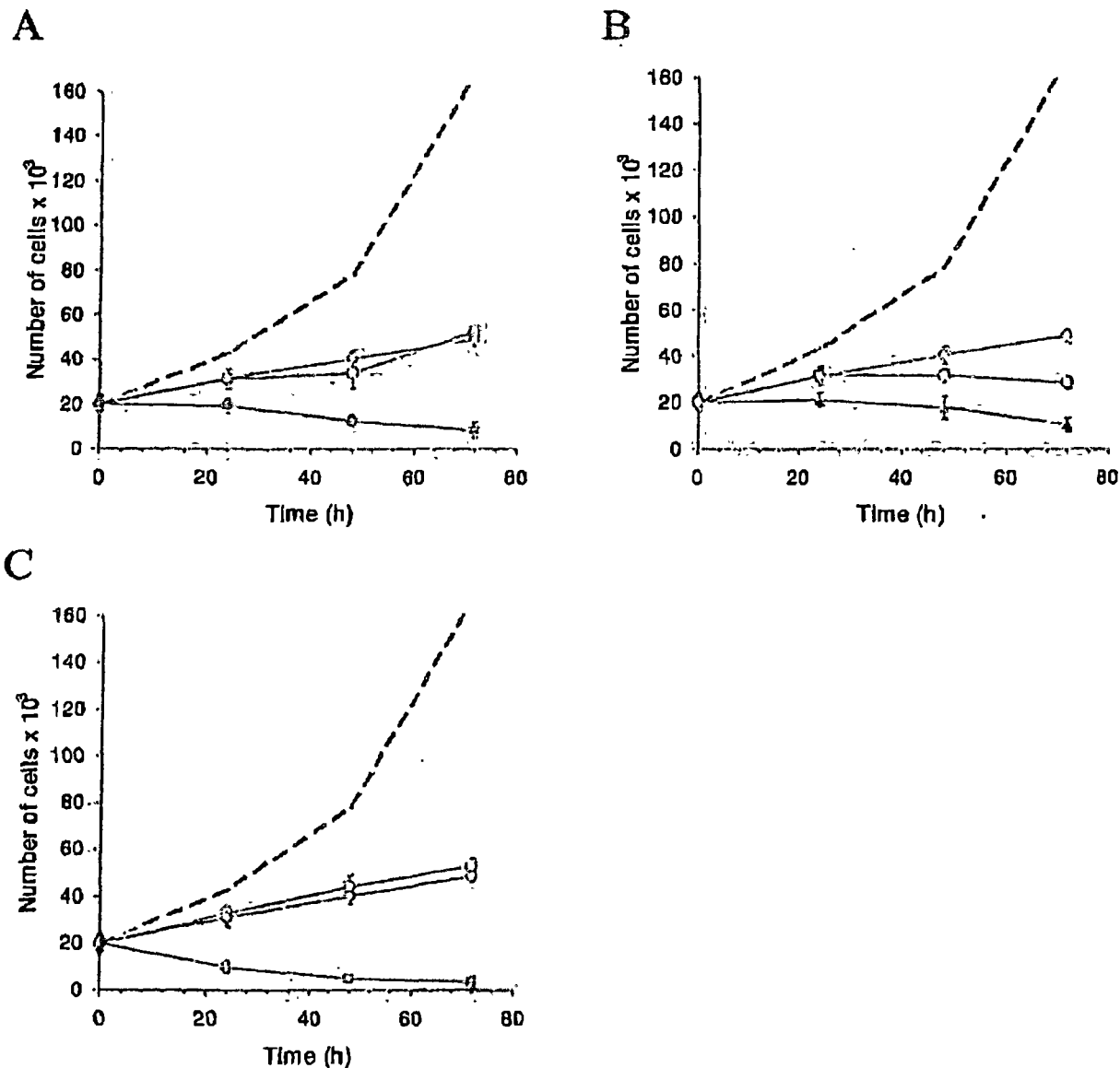
Chemotherapy	IC ₅₀ (drug alone)	IC ₅₀ (drug-TTFields combination)
Paclitaxel	5.00 nM	0.005 nM
Doxorubicin	0.04 μM	0.002 μM
Cyclophosphamide	6.60 mM	0.044 mM

**Figure 1**

Effect of 72 hour continuous application of TTFields and chemotherapeutic agents, separately and in combination on the cell proliferation of ER-negative MDA-MB-231 cells (presented as percent viable cells compared to control). (A) Percent viable cells vs. TTFields intensity. Effect of different concentrations of paclitaxel (B), doxorubicin (C) and cyclophosphamide (D), alone and in combination with TTFields of 1.75 V/cm. In B, C and D Filled Circles – represent drug alone; Filled Squares – drug in combination with TTFields. Each point represents mean values \pm SEM of 18 to 36 replicate measurements. Dotted lines demarcate the IC₅₀ values for each curve.

controls. The proliferation rate (slope of the graph) recovers almost completely during the following 48 hours, except for doxorubicin, where recovery is slower and

delayed by about 24 hours. In contrast, addition of TTFields to any one of these chemotherapeutic agents results in irreversible and complete inhibition of cell pro-

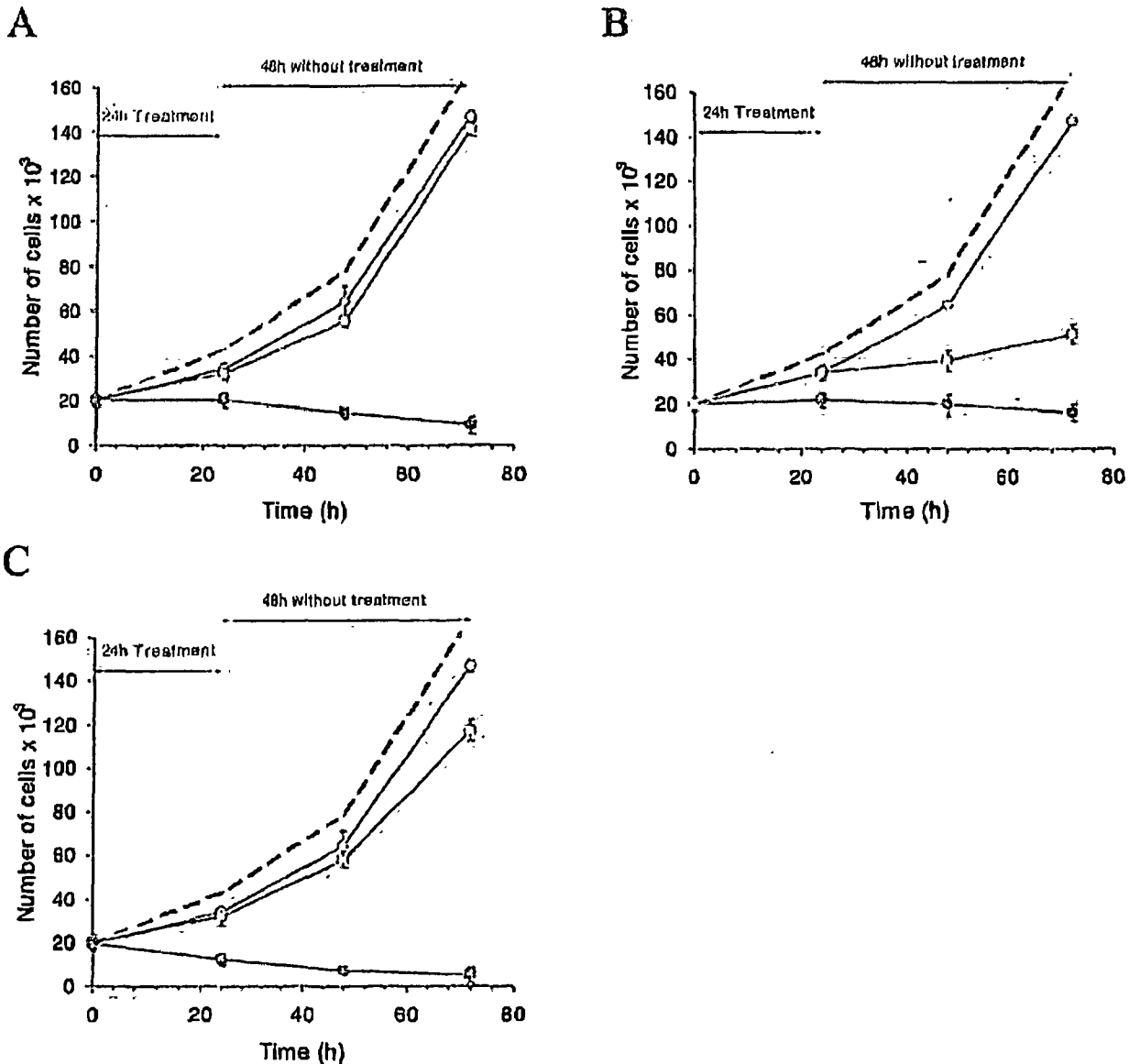
**Figure 2**

Time course of the effects of 72 hour exposure of MDA cells to Paclitaxel (A), Doxorubicin (B) and Cyclophosphamide (C) alone and in combination with 1.75 V/cm TTFields. Each graph shows the number of viable cells in culture over time in control cells (Interrupted lines), drug alone (open squares), TTFields alone (open circles) and drug-TTFields combination (closed squares). Data are presented as mean \pm SEM. Each experimental condition included 18-36 samples.

liferation rate manifested as a decrease in the number of cells in culture. For Cyclophosphamide there is an almost complete loss of viable cells after 72 hours of combined treatment.

Glioma cell cultures

Combined effect of DTIC and TTFields in human glioma cell cultures
In order to assess the combination between Temozolomide and TTFields in glioma cells, DTIC and TTFields

**Figure 3**

Time course of recovery from 24 hour exposure to Paclitaxel (A), Doxorubicin (B) and Cyclophosphamide (C) alone and in combination with 1.75 V/cm TTFields. Each graph shows the number of viable cells in culture over time in control cells (interrupted lines), drug alone (open squares), TTFields alone (open circles) and drug-TTFields combination (closed squares). Data are presented as mean \pm SEM. Each experimental condition included 18–36 samples.

were applied alone and in combination to U-118 cells in culture. Both DTIC and Temozolomide act through a common degradation product (MTIC). Thus light activated DTIC was used for these experiments as described

previously [15,16]. Figure 4 compares the DTIC dose-response curve, with that obtained with DTIC - TTFields combination. As we have shown in breast cancer cultures, the addition of TTFields to a chemotherapeutic agent

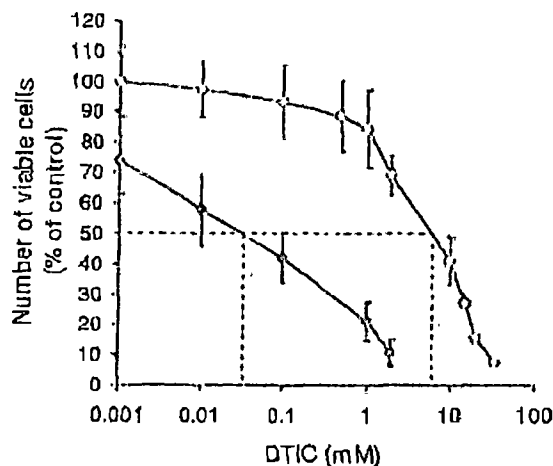


Figure 4
Effect of light activated DTIC and TTFIELDS (1.75 V/cm) on cell proliferation of U-118 glioma cells, presented as percent of viable cells compared to control. Open Circles – 72 hours of DTIC treatment alone. Filled Circles – 72 h of Combined DTIC – TTFIELDS treatment.

causes a leftward shift in the dose-response curve in glioma cells as well. The IC_{50} for DTIC alone in Figure 4 is 6.4 mM, whereas the IC_{50} for combined DTIC-TTFIELDS is two orders of magnitude lower (0.023 mM).

Analysis of combination efficacy and sensitivity in-vitro Combination indexes

The mode of interaction between TTFIELDS and chemotherapeutic agents (synergism, additivity or antagonism) can be analyzed using Combination Indexes (CI) as described by [10,17]. In order to calculate the CIs for TTFIELDS-Chemotherapeutic agents, the extent of inhibition of cell growth was assessed after 24 hours of treatment with Paclitaxel, Doxorubicin and Cyclophosphamide alone or in combination with different intensities of TTFIELDS (0.625–1.75 V/cm; see Materials and Methods). Table 2 demonstrates that for breast cancer cells the CI for Doxorubicin is very close to 1, indicating additivity [10,11]. In contrast, for TTFIELDS with Paclitaxel and Cyclophosphamide the CIs are <1 indicating additivity with a tendency towards synergism.

Dose reduction indexes

In order to assess the extent of possible chemotherapeutic dose reduction when applied in combination with TTFIELDS, dose reduction indexes (DRI) for each drug-TTFIELDS combination were calculated based on the meth-

Table 2: Calculated Combination Indexes for human breast cancer (MDA-MB-231) cells treated with paclitaxel, doxorubicin or cyclophosphamide in combination with TTFIELDS.

TTFIELDS intensity (V/cm)	Combination Index		
	MDA-MB-231 cells		
	Paclitaxel	Doxorubicin	Cyclophosphamide
	CI_{40}	CI_{50}	CI_{50}
0.625	-	-	0.74
1.25	0.97	0.99	0.84
1.75	0.86	0.98	0.95

odology described by [11]. The DRIs for TTFIELDS-drug interaction after 72 hours of combined treatment was 1316 for paclitaxel, 23 for doxorubicin, 152 for cyclophosphamide and 175 for DTIC (in U-118 glioma cells). Thus a significantly reduced dose (1–3 orders of magnitude lower drug concentration) may be used in combination with TTFIELDS to achieve the same level of efficacy.

Effect of combined paclitaxel and TTFIELDS on VX2 tumors in rabbits

Prior to testing the combined efficacy of paclitaxel and TTFIELDS on VX2 tumors implanted within the kidneys of rabbits, the dose-response of paclitaxel in this animal tumor model was determined. A dose of Paclitaxel leading consistently to a 15–20% inhibition in tumor growth (5 mg/rabbit) was chosen for subsequent combination experiments with TTFIELDS.

As seen in Figure 5, untreated tumors increased in volume by a factor of 70 from baseline. Paclitaxel treated tumors grew by a factor of 58 from baseline, TTFIELDS treated tumors grew by a factor of 34 from baseline and tumors treated by TTFIELDS-Paclitaxel combination grew by a factor of 22 from baseline. Thus the TTFIELDS-Paclitaxel combination treatment inhibited tumor growth by 69% compared to the growth of control tumors, while Paclitaxel alone inhibited tumor growth by 15% compared to the growth of control tumors, and TTFIELDS alone by 53% compared to the growth of control tumors. Thus, additivity was seen between TTFIELDS and Paclitaxel at the intensity and concentration used. Differences between curves were statistically significant ($p < 0.01$; ANOVA).

Pilot clinical trial in GBM patients

Twenty patients with histological diagnosis of GBM were treated continuously for an average of 1 year (range 2.5–24 months). Ten recurrent GBM patients were treated with TTFIELDS alone as salvage therapy. Ten newly diagnosed

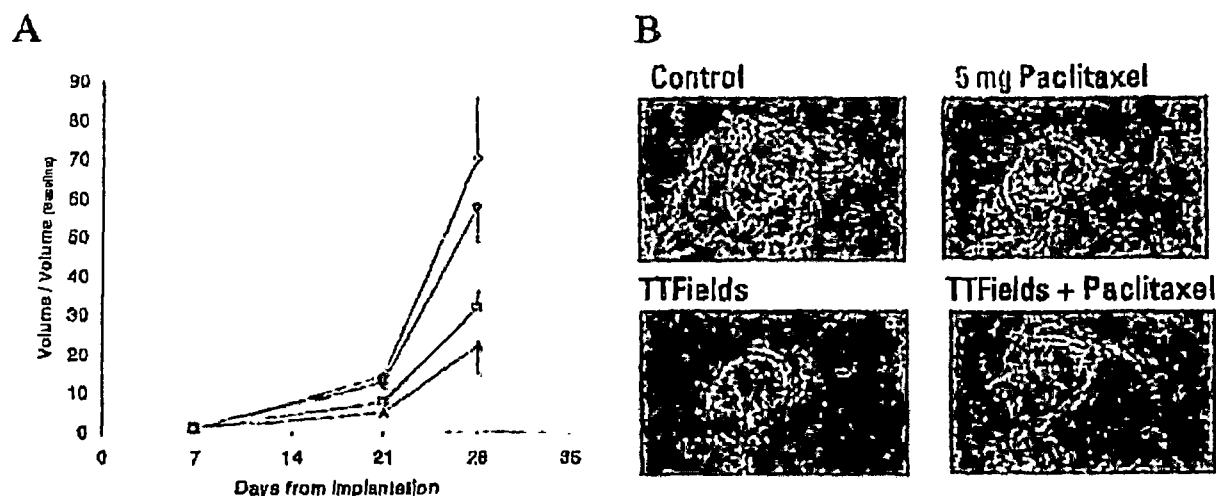


Figure 5
Effect of combined Paclitaxel/TTFields on VX2 tumors in Rabbits. A VX-2 Kidney tumor volumes were normalized to pre-treatment tumor volume (day 7) and are presented over time for: control (diamonds), 5 mg Paclitaxel (circles), TTFields (squares) and combined TTFields-Paclitaxel (triangles). The effect of combined TTFields and Paclitaxel is equal to the sum of the effects of either treatment alone at both time points measured during the study (2 and 3 weeks from treatment start; $n = 23$; bars are standard errors of means). B Exemplary MRIs of the maximal contrast enhancing tumor area (demarcated by orange borders) in the kidneys of rabbits in each of the experimental groups (sham control, Paclitaxel 5 mg, TTFields 2 V/cm, combined Paclitaxel and TTFields).

GBM patients, that had undergone surgery and thereafter received radiation therapy with adjuvant Temozolomide, were treated with the combination of TTFields in parallel to maintenance Temozolomide [14]. In both groups of patients no device related serious adverse effects were observed. The only device related toxicity reported was a dermatitis which appeared most often (18 of 20 patients) during the second month of treatment. The severity of the dermatitis decreased upon use of topical corticosteroids and periodic electrode relocation. The dermatitis continued for the duration of treatment and resolved completely within days to weeks from treatment termination.

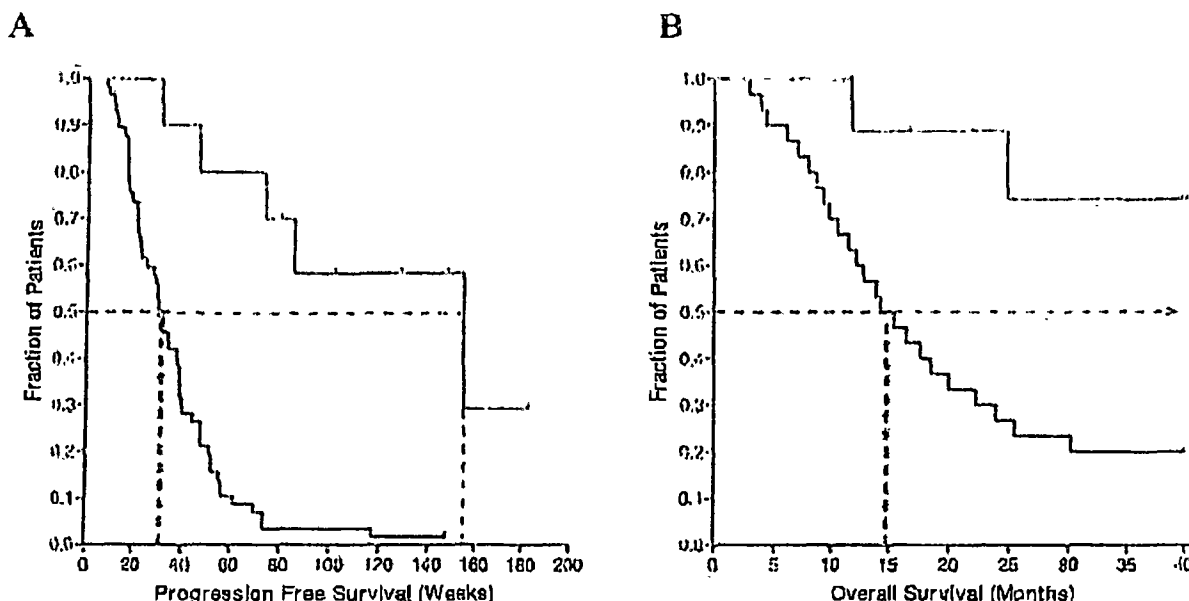
In the second group, no increase in Temozolomide related adverse events was seen due to the combination with TTFields (see Table 3).

As reported previously [1], both progression free survival (PFS) and overall survival (OS) in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively. The efficacy of the TTFields-Temozolomide combination in the second group of patients was assessed using Kaplan Meier curves [13] of PFS and OS. The Kaplan Meier curves for the PFS of these patients, treated by combined TTFields - Temozolomide are shown in Figure 6A. The median PFS of the

combination treated patients is 155 weeks versus 31 weeks for concurrent controls treated with maintenance Temozolomide alone. Note that 5 of 10 patients are currently progression free. Figure 6B compares the OS of the patients that received the combination treatment (Red line) with a matched historical control (KPS>60, Median age 54) (Black line [14]). It is seen that for the TTFields - Temozolomide combination treated patients, the Median OS > 39 months versus about 14.7 months for matched historical control patients who received maintenance Temozolomide alone. It should be noted that at the time

Table 3: Toxicities by grade and causality in the newly diagnosed GBM patients treated with combined TTFields-Temozolomide.

	Grade		Causality assessment
	I-II	III-IV	
Elevated LFTs	6/10	0/10	Anti Epileptic Drugs
Hyperglycemia	4/10	0/10	Oral Steroids
Anemia	6/10	0/10	Temozolomide
Thrombocytopenia	2/10	0/10	Temozolomide
Leucopenia	3/10	0/10	Temozolomide
Headache	2/10	0/10	Underlying disease
Seizures	1/10	0/10	Underlying disease
Dermatitis	10/10	0/10	NovoTTF-100A

**Figure 6**

Kaplan Meier curves for **A** – progression free survival (PFS) and **B** – overall survival (OS) of newly diagnosed GBM patients receiving either combined TTFields – Temozolomide treatment or Temozolomide treatment alone. Red line – patients receiving combined TTFields – Temozolomide treatment ($n = 10$), Black line – concurrent/historical control patients that received Temozolomide treatment alone. A – The difference between the PFS curves is highly significant – Log-Rank Test ($P = 0.0002$), Hazard Ratio 3.32 (95%CI 1.9–5.9). B – The difference between the OS curves is highly significant – (Log-Rank Test; $P = 0.0018$). Dashed lines mark the median values for each curve.

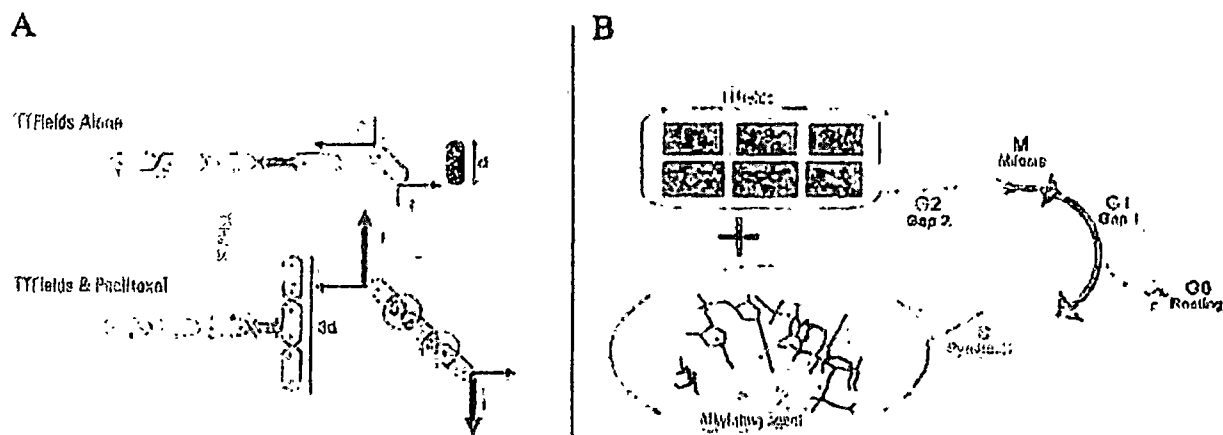
of this report 8 of 10 patients, receiving the TTFields-Temozolomide combination treatment, are alive.

Discussion

Cancer treatment with drug combinations was introduced in order to improve therapeutic indexes through dose reduction of each drug and increase treatment efficacy. In this study the exposure of cancer cells to combined chemotherapy and TTFields was studied in cell cultures, an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients. The results of this study support the possibility that TTFields may be used, not only as an effective stand alone anti-proliferation agent (as shown previously in [1]), but also as an effective adjuvant that enhances chemotherapy efficacy without an increase in toxicity. In addition to this increase in efficacy, these results raise the possibility of dose reduction of chemotherapy when used in combination with TTFields. This is of utmost importance since, at tolerable doses the efficacy of available cancer therapeutic agents is often far from optimum while being associated with a high degree of toxicity.

With regards to the mechanisms involved, one may assume that tumor cells are sensitized to TTFields by chemotherapy, much like another well established physical therapy – ionizing radiation [8,18,19]. In the specific case of Paclitaxel, one of the most commonly used treatments for late-stage human breast cancer [20], the combined effect may be attributed to their similar site of action – the spindle microtubules [1,2,21]. Taxanes act by stabilizing the link between individual tubulin dimers [21]. As illustrated schematically in Figure 7A taxanes increase the length of tubulin filaments within the cell. One of the mechanisms of action of TTFields is the misalignment of mitotic spindle filaments as a result of TTFields forces on tubulin chains [2]. The increase in filament length due to taxanes, increases the dipole moment of these macromolecules, leading to an increase in the TTFields induced forces and thus to a higher sensitivity of the cell to TTFields (see Figure 7A).

Doxorubicin that has a broad spectrum of activity both in experimental tumor models and in human malignancy, affects both DNA and RNA synthesis [22]. Cyclophosphamide (an alkylating agent) inhibits DNA replication by

**Figure 7**

Mechanisms of potentiation of chemotherapeutic efficacy by TTFields. A Tubulin chains are elongated by Paclitaxel, leading to an increase in the average dipole moment of free tubulin chains (d – length of an individual tubulin dimer; f – force between the microtubule chain and the dimer; F – force acting on the tubulin dimmers by TTFields; Arrow length is proportional to the intensity of these forces). The forces TTFields exert on these larger dipoles, F , are enhanced leading to an increase in the disruption of the mitotic spindle by TTFields. B TTFields act as an M-phase inhibitor, while alkylating agents act at the G and S phases of the cell cycle. This separation between cell cycle phases affected explains the additivity seen experimentally.

interfering with the separation of the double stranded DNA essential for transcription [23]. As illustrated in Figure 7B, since TTFields act at a completely different stage (M phase) of the cell cycle from both these agents, additivity between chemotherapy and TTFields can be expected.

Since the data for newly diagnosed GBM patients, which points to well over a 300% increase in PFS and OS, was obtained only with combination treatment, one cannot directly separate the TTFields effects from the chemotherapeutic effect. However, if we assume that the TTFields therapeutic efficacy for newly diagnosed patients is similar to recurrent GBM, i.e. the median of OS is increased by 270% [1] while the published Temozolomide data indicates an increase of about 20% in OS compared to ionizing radiation treatment alone [14], the results presented in Figure 6 point towards additivity between TTFields and Temozolomide. It is important to note that this significant increase in efficacy was obtained without any increase in device or drug related toxicity (see table 3).

An additional important finding is that both 24 h and 72 h combination treatments in-vitro result in severe irreversible cellular damage in contrast to chemotherapy alone. This result strengthens the assumption that combination therapy with TTFields may be much more effective than treatment by individual agents.

Conclusion

The results of the present study support the notion that TTFields may be used clinically not only as an anti-proliferation agent as shown before [1], but also as effective sensitizers of currently used chemotherapeutic agents. Such sensitization was not shown to be associated with any additional systemic toxicity. Moreover, as demonstrated by the high DRIs calculated in this study, chemo/TTFields combinations are expected to provide the same or even greater therapeutic efficacy with much lower drug concentrations thus lowering further the overall toxicity.

Competing interests

EK, RSS, AI, DM, ZG, ES and YW are employees of NovoCure Ltd.

YP has a minority holding in NovoCure Ltd.

VD, FT, JV and DG have no competing interests.

Authors' contributions

EK – planned the pre-clinical and clinical experiments, supervised their execution, analyzed results and wrote parts of the manuscript. RSS and ET – Performed the in-vitro experiment and assisted in the in-vivo experiments. DM, ZG and AI – Performed the in-vivo experiments. DG – Performed the MRI imaging for the in-vivo experiments. YW – Planned the medical devices and treatment parameters.

ters for all experiments. VD, FT and JV – performed the clinical trial in GBM patients (clinical investigators). YP – invented the concept of TTFields, helped interpret all results and wrote the majority of the manuscript.

Appendix

Appendix A – Eligibility criteria for the pilot GBM trial

Inclusion criteria:

Histologically proven diagnosis of GBM.

Age over 18 years.

Karnofsky scale ≥ 70 .

Participants of child bearing age had to be receiving efficient contraception.

Willing and able to sign an informed consent prior to participation in the study.

Exclusion criteria:

Patients actively participating in another clinical trial

Patients who received any anti-tumor therapy in the four weeks prior to trial initiation (steroids are permitted; however, the dose must be stable or decreasing during the trial).

Patients suspected of suffering from radiation necrosis (according to a PET scan).

Pregnancy

Patients with one of the following co-morbidities:

Patients with an implanted pacemaker or documented arrhythmias.

Significant renal, hepatic or hematologic disease.

Significant additional neurological disorder;

Seizure disorder unrelated to the patient's tumor

Pre-existing dementia

Progressive degenerative neurological disorder

Meningitis or encephalitis

Hydrocephalus associated with increased intracranial pressure (ICP)

Acknowledgements

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Expert Opinion

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Tumor treating fields: concept, evidence and future

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Introduction: Local control is fundamental, both for the curative as well as the palliative treatment of cancer. Tumor treating fields (TTFields) are low intensity (1 – 2 V/cm), intermediate frequency (100 – 200 kHz) alternating electric fields administered using insulated electrodes placed on the skin surrounding the region of a malignant tumor. TTFields were shown to destroy cells within the process of mitosis via apoptosis, thereby inhibiting tumor growth. TTFields have no effect on non-dividing cells.

Areas covered: This article reviews *in vitro* and *in vivo* preclinical studies, demonstrating the activity of TTFields both as a monotherapy as well as in combination with several cytotoxic agents. Furthermore, it summarizes the clinical experience with TTFields, mainly in two indications: one in recurrent glioblastoma multiforme: in a large prospective randomized Phase III trial TTFields was compared with best standard care (including chemotherapy): TTFields significantly improved median overall survival (OS) compared with standard therapy (7.8 vs 6.1 months) for the patients treated per protocol. Importantly, quality of life was also better in the TTFields group. The second indication was a Phase II study in second-line non-small cell lung cancer, where TTFields was administered concomitantly with pemetrexed. This combination resulted in an excellent median OS of 13.8 months. Interestingly, the progression-free survival (PFS) within the area of the TTFields was 28, however, outside the TTFields the PFS was only 22 weeks.

Expert opinion: The proof of concept of TTFields has been well demonstrated in the preclinical setting, and the clinical data seem promising in various tumor types. The side effects of TTFields were minimal and in general consisted of skin reaction to the electrodes. There are a number of ways in which TTFields could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible. While more clinical data are clearly needed, TTFields is an emerging and promising novel treatment concept.

Keywords: cancer, electric fields, glioblastoma, non-small cell lung cancer, TTFields

Expert Opin. Investig. Drugs [Early Online]

1. Background

Alternating electric fields have been used since many years for the diagnosis, research and treatment of various medical conditions. Such electric fields have different properties, depending on their frequency and intensity (Table 1). Very low frequencies (lower than 1 kHz) are used to excite the membrane of muscles and nerves, thereby leading to membrane depolarization and finally to action potentials (1-3). Higher frequency alternating electric fields penetrate cells better, but the overall effect of hyper-depolarization on the cell membrane balances in a way that the integrated stimulation does not yield an action potential. However, at frequencies higher than 10 MHz, the electrophysiological properties of the eukaryotic

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Article highlights.

- Tumor treating fields (TTFields) are low intensity (1 – 2 V/cm), intermediate frequency (100 – 200 kHz) alternating electric fields, which can induce apoptosis.
- TTFields are able to inhibit tumor growth in various cell lines and animal models.
- The combination of TTFields with several cytotoxic agents resulted in a supra-additive tumor growth inhibition *in vitro* and *in vivo*.
- Two clinical trials, a Phase III trial in glioblastoma multiforme (GBM) and a Phase II study in non-small cell lung cancer (NSCLC) have shown antitumor activity of TTFields.
- Toxicity was low; it consisted mainly of skin reactions at the site of the electrodes.

This box summarizes key points contained in the article.

membrane lead to dielectric polarization that eventually heats the tissue (4,5). Intermediate-frequency alternating electric fields, at frequencies between 10 kHz and 1 MHz, neither cause net depolarization nor significant dielectric losses, therefore, cannot stimulate nerves/muscles, but also cannot seriously heat tissues at low enough intensities. It was thought that such electric fields have no meaningful biological effect on cells (4,6-9). Nevertheless, it was recently found that such fields, named tumor treating fields (TTFields), have an anti-mitotic activity and may lead to the death of dividing cells. The fields were found to have these properties already at a very low intensity (< 2 V/cm) and at intermediate frequency of 100 – 300 kHz.

2. TTFields's mechanism of action

Each cell contains numerous electrically charged molecules, such as proteins and DNA. Under an alternating electric field, these molecules will oscillate according to the changing direction of the field and its density (Figure 1). If the field is uniform, the forces acting intermittently to opposite directions will cause a movement parallel to the direction of the field. When the frequency of the field is high enough, such as in the case of TTFields, this molecular movement will reduce. In the case of dipoles, where there is an electric split between the positive and negative poles of a molecule, it will align with the direction of the electric field and remain at the same place. All charged molecules, including dipoles, will move toward the higher field density in a non-uniform alternating electric field. Within a non-dividing cell, the field is mostly uniform and the net force on charges and dipoles will, therefore, yield minimal movement. Non-uniform electric fields, on the other hand, force polar molecules to move toward higher field intensity, in a process called dielectrophoresis (10,11). Such fields are characteristic of dividing cell when a narrow furrow connects the two forming daughter cells.

2.1 Arrest of mitotic spindle formation

Mitotic spindle is the organelle that separates the cell's chromosomes to each of the daughter cells during mitosis. The arms that hold to the chromosomes consist of small polar molecules called tubulins, which polymerize to form a 'chain' of subunits that will reach the genetic material at the center of the cell. As noted before, the field is uniform within the non-dividing cells, but the tubulin subunits will tend to align according to the direction of the field. Finite element simulations showed that the electrical forces acting on the subunits prevent them from attaining the orientation required for efficient polymerization, therefore, mitosis becomes arrested for an abnormally long time (12). This happens since subunits far enough from the growing microtubule will be subjected to an electric force strong enough to prevent further polymerization. When this process takes place, cells could either complete mitosis or disintegrate.

2.2 Mitotic furrow destruction

Not all cells seem to be affected by means of disruption of mitotic spindle formation. The membranes of cells that completed metaphase will start dividing into two daughter cells, pulling the daughter chromosomes to each of the cells' poles. During the last step in mitosis, that is, cytokinesis, a cleavage furrow is eventually formed, which completes the process of cell separation. This narrow membranous link results in an hourglass-shaped non-uniform electric field, unlike non-dividing cells, in which the electric field is uniform. During cytokinesis, the densest electric field is found in the narrow center. This focusing of the field directs all electric charges and dipoles to the furrow due to the unidirectional character of the electric force (dielectrophoretic force) under this condition. Finite element simulations have shown that polarized molecules and organelles within the cell will be affected by forces high enough to move toward the furrow so as to disrupt the internal cell structure and cause the cell destruction seen under TTFields therapy (12).

3. Preclinical studies with TTFields

A number of preclinical trials have shown the efficacy of TTFields in the inhibition of cancer cell proliferation and their destruction *in vitro* (12,13). Many cell lines were cultured and tested under TTFields, among others melanoma, glioma, lung, prostate and breast cancers. TTFields was applied continuously for 24 – 72 h, in all cases, proliferation was significantly inhibited, compared with control cultures and to non-replicating cultures (baby hamster kidney (BHK) cells) treated with TTFields. For some of the cell lines, a specific optimal frequency that demonstrated maximal inhibitory effect was found, possibly reflecting different cell size and shape (Table 2) (13). Under time-lapse microscopy, cancer cells demonstrated significantly prolonged mitosis and even cell destruction on the formation of the cleavage furrow. Immunohistochemistry studies of cell cultures treated with TTFields showed many abnormal

Table 1. Alternating electric fields used in medicine

Frequency	Biological activity	Application
< 1 kHz	Membrane depolarization	Defibrillators, ECT, bone growth, fracture healing, ICD
100 – 300 kHz	Mitotic arrest and apoptosis	TTFields
1 – > 10 MHz	Dielectric polarization	Diathermy, radio frequency tumor ablation

ECT, electroconvulsive therapy; ICD, implantable cardioverter-defibrillator; TTFields, tumor treating fields.

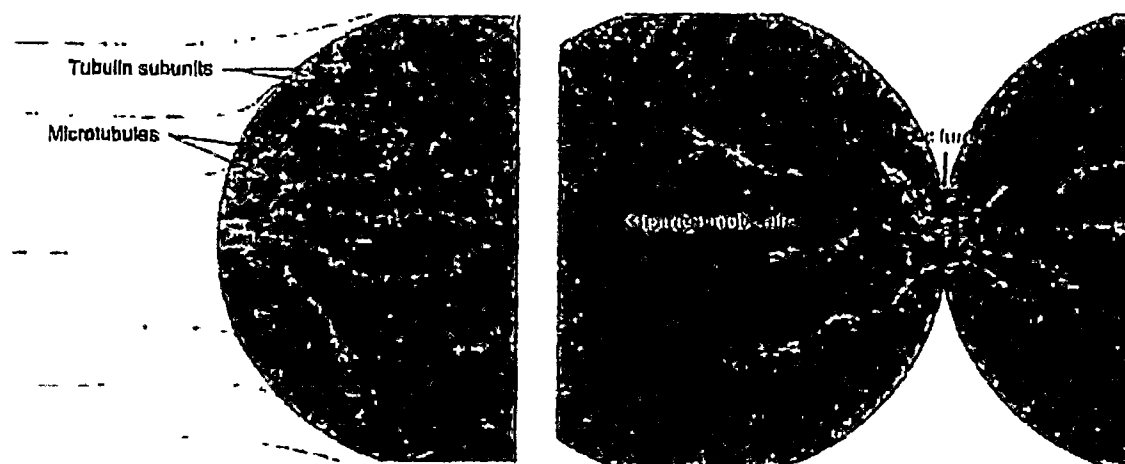


Figure 1. Antimitotic effects of tumor treating fields (TTFields). At the beginning of mitosis, the electric field is uniform within the cell, causing tubulin subunits to align with the direction of the field and inhibiting their polymerization to form a normal microtubule spindle. In a non-uniform electric field formed during cytokinesis, charges and dipoles move toward the high field density at the mitotic furrow, disrupting mitosis and disintegrating the daughter cells.

mitotic figures that could be related to the interference of TTFields with the mitotic spindle formation. These figures resemble the presentation of cancer cells treated with agents that interfere with mitotic spindle formation, such as paclitaxel. Further experiments showed that the efficacy of TTFields in combination with different chemotherapies is additive and could be synergistic (14).

Interestingly, TTFields caused cultured cells to orient in the direction of the electric field (12). This could be explained by the fact that the electric forces are maximal when the axis of division is aligned with the external field. This also implies that the angle of the cell affects its vulnerability to TTFields during mitosis.

TTFields was also shown to inhibit tumor growth in several mouse, rat and rabbit animal models (12,13). Implanted cell lines were used to test the most effective frequency and intensity for this *in vivo* treatment. Postmortem analysis of the treated animals showed a significant tumor size reduction in the case of TTFields-treated animals, compared with control animals. No difference of the local temperature in the vicinity of the tumor was found between the two groups. *In vivo* experiments showed that it is possible to deliver the field to the target region using

insulated non-invasive electrodes. While there was no statistically significant inhibition of tumor growth when a unidirectional TTFields was delivered this way, two- and three-directional fields led to a statistically significant growth inhibition (13). *In vivo* tumor models have shown the same optimization in tumor inhibition when using the effective specific frequency for each cell type. No abnormality in vital signs, electrocardiograms (ECG), complete blood counts (CBC), chemistry and coagulation panels was found during the follow-up period of animals treated with TTFields, and no treatment-related pathologies were found postmortem.

In a metastatic melanoma mouse model and metastatic kidney cancer rabbit model, TTFields was shown to reduce the extent of metastatic spread, possibly due to metastasis growth inhibition, migration capability impairment and primary tumor local control (13).

4. Clinical studies with TTFields

Prior to applying TTFields to human patients, feasibility was tested using finite element mesh (FEM) simulations and measurements within the brain of a volunteer undergoing brain

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Table 2. Optimal TTFields frequency for tested cell lines

Cell line	Optimal frequency (kHz)
B16F1 (mouse melanoma)	120
AA8 (Chinese hamster ovary)	150
VX-2 (rabbit kidney)	150
MCF-7 (human breast)	150
MDA-MB-231 (human breast)	150
F-98 (rat glioma)	200
U-87 (Human glioma)	200
U-118 (Human glioma)	200

TTFields, tumor treating fields.

surgery. It was found that TTFields can be effectively applied to the cerebrum using surface electrodes. TTFields was first tested on 10 recurrent malignant glioblastoma multiforme (GBM) patients. No concomitant chemotherapy was used during the clinical trial, and TTFields was the only antitumor therapy. TTFields was delivered via a portable, light-weight (~ 3 kg) device carried by the patient (NovoTTFields-100A, NovoCure Ltd, Haifa, Israel), connected to two pairs of insulated electrodes that were applied to the patients' skin. The device continuously (18 h/day on average) delivered two perpendicular 1–2 V/cm, 200 kHz alternating electric fields (Figure 2). Patients had a highly significant increase in the median time to disease progression (26.1 weeks) and progression-free survival (PFS) at 6 months (50%) compared with historical controls, with a median overall survival (OS) of more than 62 weeks [13]. In addition, no treatment-related serious adverse event was detected in a total of 280 treatment weeks. The only treatment-related adverse event was mild-to-moderate contact dermatitis beneath the electrode gel, which was easily managed using topical treatments.

These preliminary findings led to a Phase III clinical trial of TTFields compared with best standard of care chemotherapy in 237 patients with recurrent GBM [16,17]. Patients in this study were previously treated with an unlimited number of surgeries/chemotherapy cycles. They were randomized to either a TTFields arm, given as a monotherapy without additional antitumor treatments, or to the best standard chemotherapy (BSCh) arm, which was at the treating physician's discretion. TTFields was administered continuously and patients' compliance was excellent, with a median duration of 20 h/day. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. Mean treatment duration was 4.4 months in the TTFields group versus 2.3 months in the BSCh group. In the group of 185 patients who were treated per protocol, a statistically significant survival benefit was seen for the TTFields group (median OS 7.8 vs 6.1 months for TTFields and BSCh, respectively). Moreover, patients with better prognostic baseline characteristics (KPS 80% or higher, age 60 or lower) demonstrated an even higher survival benefit when treated with TTFields (median OS 8.8 vs 6.6 months; $n = 110$). These results show that TTFields

as a monotherapy are at least as effective as the best available chemotherapy or supportive care in this poor prognosis disease. It is noteworthy that quality of life (QOL) was equivalent or superior in patients treated with TTFields compared with BSCh. This clinical trial also showed that the only TTFields-related adverse events were mild-to-moderate contact dermatitis beneath the electrodes in a minority of patients. The incidence of toxicities was significantly higher in the BSCh arm.

TTFields was also explored in a Phase III single arm study in combination with pemetrexed for advanced (stage IIIB/IV) non-small cell lung cancer (NSCLC) as a second-line treatment; after failure of standard first-line chemotherapy [18]. Electrodes were applied to the chest and upper abdomen and the device (NovoTTFields-100 L, NovoCure Ltd) generated 150 kHz TTFields, in accordance with the preclinical findings relating to lung cancer cell lines. Forty-one patients were treated, including 7 (17.1%) with squamous cell carcinoma and 30 (73%) with stage IV disease. The device was well tolerated and the average daily use was 11.2 h. No TTFields-related serious adverse event was reported for a cumulative time of over 720 weeks. Median PFS was 22 weeks and in-field PFS (i.e., PFS within the area of the TTFields; the study's primary end point) in the lungs and liver was 28 weeks. This is an important finding because it can be assumed that in the same patient the higher tumor control within the TTFields area was a specific effect of TTFields. Median OS was 13.8 months and 1-year survival was 57% (Figure 3). Six patients (14.6%) had a radiological partial remission (PR) and 16 patients had stable disease (SD) (39%). These results are very promising and compare extremely well with matched historical controls treated with pemetrexed alone in second-line treatment [19].

Special attention was given to potential adverse events using TTFields: in the glioblastoma trial careful neurological examination and documentation was required once a month. In the lung cancer trial, ECGs were mandated at the beginning of the trial, during the treatment if adverse effects occurred and at the end. Finally, skin reactions were monitored at every visit and documented according to the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC) (version 3.0) in all studies. All other adverse events were monitored routinely at every visit according to the CTC criteria. In all studies involving TTFields the only side effect, which occurred more frequently was grade 1–2 skin toxicity. In the glioblastoma trial there was a direct control group, in the lung cancer trial we compared the side effects with the large Phase III study by Hanna *et al.*, in which pemetrexed was given as a second-line treatment [19].

5. Summary

TTFields was shown to inhibit proliferation and to cause cell destruction of many cancer cells *in vitro* and *in vivo*. In addition, TTFields significantly improved human patients' prognosis in recurrent GBM and probably also in NSCLC. At the time this review was submitted, there were no serious adverse events found related to TTFields.

The good safety profile along with the significant clinical efficacy and QOL advantages make TTFields an attractive treatment in GBM, and perhaps in many other malignancies.

TTFields is a novel and promising concept for treating solid tumors. *In vitro* and *in vivo* experiments have repeatedly shown a significant inhibitory effect on cancer cell proliferation upon application of TTFields. We already know that at least two physical mechanisms are involved; the first is interference with the mitotic spindle formation as a result of electric forces preventing the normal polymerization of the tubulin subunits. The second mechanism results from the non-uniformity of the electric field in the context of cytokinesis, and the movement of molecules in the direction of the mitotic furrow as a result of the unidirectional force generated by TTFields.

There are also some data indicating that combining chemotherapeutic cancer treatments with TTFIELDS may increase efficacy and sensitivity to chemotherapy [14]. Several tumor types are sensitized to radiation after adding different chemotherapies, even at low doses [24-26]. Could some tumors similarly be more susceptible to TTFIELDS treatment if treated concomitantly with certain cytotoxic agents? This is a plausible idea, since TTFIELDS acts on specific organelles (e.g., the mitotic spindle), which are also the target of some of the anticancer drugs. Taxanes act through stabilizing the link between tubulin dimers in the spindle microtubules. It could be that the abnormal increase in microtubule length caused by this class of agents, which leads to the formation of a larger dipole moment, results in an increase in the efficacy of TTFIELDS [14]. This possible synergism could be used to achieve a better response, but alternatively also as a way to decrease chemotherapy intensity in patients who cannot tolerate the toxicity of full-dose chemotherapy. The fact that TTFIELDS itself was not toxic and in combination with paclitaxel did not increase the known side effects of the latter in the clinical trials mentioned above, makes combination therapies an attractive therapeutic option.

Preclinical experiments showed the frequency-dependant effect of TTFields, with different frequencies showing a maximal inhibitory effect in certain cancer cell types (13). In the future, it will be interesting to see how this characteristic could be exploited in order to maximize the effect, by adjusting the frequency on an individual tumor basis, using cytological/pathological specimens for the analysis. Such adjustments could be possible for tumors of the same entity but in different patients, and maybe even at different stages in the course of the same disease.

Other fields of interest that will probably be investigated in the future include the pathway in which cell death occurs following exposure to TFFs. Unpublished findings show that apoptosis is the process that leads to cancer cell death



Figure 2. The tumor treating fields (TTFields) generating portable device (NovoTTFields-100A).

On the contrary, the treatment was toxicity-free for treated patients, except for mild-to-moderate contact dermatitis underneath the electrodes. Importantly, there were no cardiac or neurological abnormalities as a result of TFields treatment. The use of non-invasive surface electrodes prevented flow of ionic currents [20,21] or cell death [22] as a result of direct currents, and thus decreased skin damage and enabled continuous treatment.

TTFields can actively inhibit different cell types, including multi-drug-resistant (MDR) ovarian and breast cancer cell lines that overexpress ABC (ATP-binding cassette) transporters [28]. It may not only be useful in the treatment of locally advanced tumors, but also in the prevention and treatment of metastatic disease. TTFields has the potential to inhibit the migration of metastases from a primary tumor, it can inhibit the growth of metastases in the lungs once they have been seeded in the target organ, through the presence of the fields in the lungs themselves.

In the first Phase III study published to date [16,17], TTFields had minimal toxicity and patients' compliance was excellent, over an extended period of time. The application of TTFields resulted in an improved median OS, higher response rate and longer time to treatment failure compared with best standard chemotherapies and also led to an improvement in many QOL parameters. A large-scale Phase III clinical trial in newly diagnosed GBM is currently being conducted.

In the first clinical trial for NSCLC patients, TTFelds was well tolerated in a second-line setting. It was safe and efficacy

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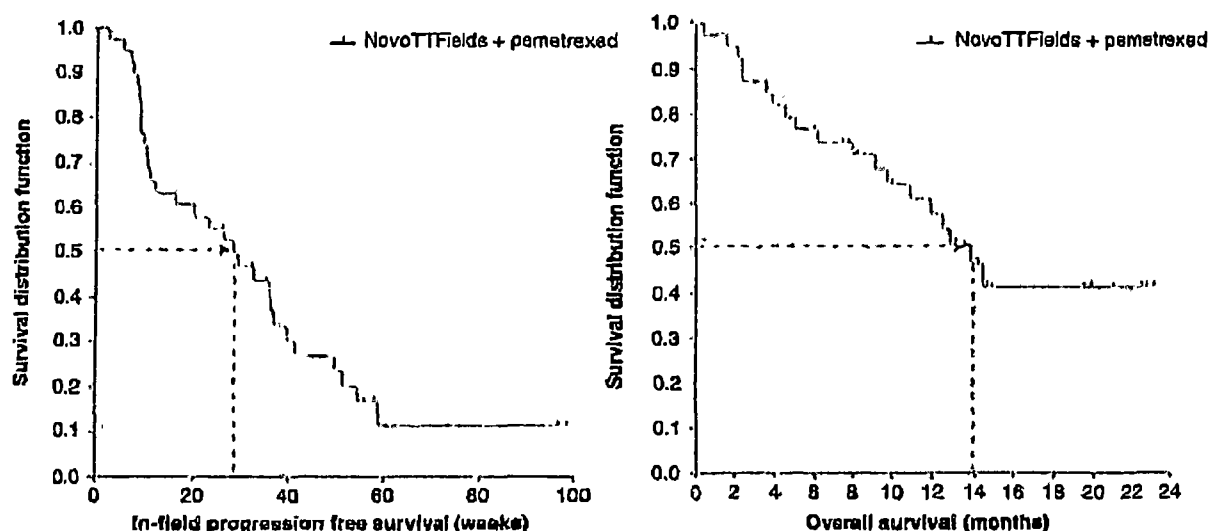


Figure 3. Phase II trial using tumor treating fields (TTFields) in combination with pemetrexed in non-small cell lung cancer as a second-line therapy. Median in-field progression-free survival (PFS) was 28 weeks. Median overall survival (OS) was 13.8 months; $n = 41$.

Adapted from poster presentation ESMO 2010 [18].

under TTFields. Finding the specific pathway through which apoptosis is carried out will provide a better understanding of the basic mechanism and will pave the way for other combinations or treatment optimization. The immune system plays an important role in the pathogenesis of cancer [27]. TTFields has the potential to beneficially affect the microenvironment of the tumor: it could act directly on recruited immune cells, alternatively, it could change the interaction between these cells and the tumor following changes to the tumor cell structure, vasculature, etc. Preliminary data show that there is a change in the presence of immune cells that interplay with cancer cells, following TTFields treatment [15].

Both the Phase III (for recurrent GBM patients) and the Phase II (for advanced NSCLC) trials have given some important insights on using TTFields [16–18]. The high compliance demonstrates that it is feasible to administer TTFields continuously using a light-weight portable device, in spite of the necessity to be attached to the device. Since most patients enrolled in the trials were somewhat hindered by their malignant disease, they generally adjusted to TTFields quite quickly and well. In the NSCLC trial, the majority of patients used TTFields overnight and was free at daytime. It can be assumed that other cancer patients will tolerate TTFields as well. It will be interesting to see how other chemotherapies administered concomitantly to TTFields will affect the course of these patients. A Phase III trial (NCT00916409) for newly diagnosed GBM patients treated with a combination of temozolomide and TTFields is currently ongoing.

As a physical treatment modality, TTFields has the potential to be active in other solid tumors as well. In a pilot study,

TTFields therapy was very well tolerated and safe for four patients bearing skin lesions from breast and melanoma tumors. These tumors showed transient inhibition in the growth rate during a 2- to 4-week treatment and the findings warrant further investigations [28]. While systemic chemotherapy usually has significant toxicities, biologically targeted therapies often affect only a subset of tumors carrying specific mutations or proteins. Glioblastoma and NSCLC, like many other tumors, harbor many different genotypes [29–31] and it has been difficult to show a major impact of chemotherapy or even targeted agents in these tumor types, at least for the majority of patients. TTFields acts independently of the expression of cell surface receptors or other tumor biomarkers. There are no alternative mitosis mechanisms, thus cancer cells are unlikely to be or to become resistant to TTFields.

There are several ways of further developing TTFields clinically. TTFields is a regional treatment: it could be employed in situations where radiotherapy is not possible anymore, for example, after a full course of radiation to the brain. Another option would be to test it in situations in which prophylactic radiotherapy is used: for example, prophylactic cranial irradiation (PCI) small cell lung cancer, hopefully circumventing the late toxicity of PCI. Lastly, it can of course be tested together with radiotherapy. Even though TTFields is a regional treatment, it still managed to decrease the likelihood of metastases formation in animal experiments [15], the most common cause of death in cancer. It could be that TTFields was able to prevent malignant cell evasion from the primary tumor in the lung cancer treated population, thereby leading to decreased formation of micrometastases [18].

In summary, TTFields could be considered as a potential effective treatment for patients suffering from different cancer types. The non-toxic characteristics and promising clinical outcomes in several clinical trials conducted to date should encourage investigators to further evaluate TTFields, either as a monotherapy or in combination with other treatments.

Declaration of interest

M Pless declares no conflicts of interest. U Weinberg works for NovoCure Ltd. as Medical Director. NovoCure has supported experiments described in this review and was the sponsor for the clinical trials. The paper was not supported by a commercial company.

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- Kirson ED, Schneiderman RS, Dbaly V, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). *BMC Med Phys* 2009;9:1.
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- Kirson ED, Gillad M, Gurvich Z, et al. Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs. *Clin Exp Metastasis* 2009;26(7):633-40.
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Tumor treating fields: concept, evidence and future

- radiosensitivity of squamous carcinoma cell lines of the head and neck. *Cancer Res* 1996;56(22):5198-204
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Affiliation

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²NovoCure Ltd,

Marim Advanced Technology Centre,

51905, Haifa, Israel

255050

PAGE 24

07/09/2013 Tue 20:44

255959



How we made our decision

1. We read all the papers in the file.
2. We checked Medicare rules.
3. We checked the contract with Anthem.
4. We sent the file to a MAXIMUS Federal Services Doctor Consultant.

To make our decision we read all the papers in the file very carefully. We used the Medicare rules. We looked to see if Anthem correctly followed Medicare rules and regulations.

Medicare rules say that the health plan must give the member a subscriber agreement. It is a contract between the health plan and the member. It is usually called the "Evidence of Coverage" (EOC) or "Member Agreement." We read this contract carefully to see what Anthem is supposed to cover.

We sent the case to a MAXIMUS Federal Services Doctor Consultant. This doctor works for us, not the health plan. We asked this doctor to review all of the medical records in the file.

Medicare rules

The rules say that health plans must pay for a medical service or item if regular Medicare would pay for it in this case. You can find this rule at 42 CFR §422.101.

The rules say that medically necessary services are those that are reasonable and necessary for the diagnosis or treatment of an illness or injury. Medically necessary services include services to improve the functioning of a malformed body member. You can find this rule at Social Security Act § 1862 (a)(1)(A).

If you want to read these Medicare rules, you can go to this web site www.medicareappeal.com.

The health plan contract

The health plan contract says that Anthem covers items and services in accordance with Medicare rules.

Doctor review

Our MAXIMUS Federal Services Doctor Consultant looked at the file for this case. This doctor says that the NovoTTF 100-A system is medically necessary for [REDACTED]. Our doctor found that the patient presented in October 2012 with headaches, confusion and left hemiparesis. A MRI scan revealed a right fronto-temporal mass that was resected by December 2012. The pathology showed this tumor was a glioblastoma multiforme, WHO grade IV. She got temozolomide and concurrent radiation therapy but the tumor progressed. She had more surgery in March 2013 after which the NovoTTF device was recommended. In 2011, the FDA approved the NovoTTF-100A device to deliver alternating electrical fields to treat recurrent GBM. The device has FDA approval and is appropriate to use in this patient who has exhausted standard chemotherapy options.

Explanation of decision

We decided that Anthem has to pre-approve the NovoTTF 100-A system (electrical field therapy)

for [REDACTED]

07/09/2013 Tue 20:44

255959



You asked Anthem to pre-approve the NovoTTF 100-A system. You say that this device is the only promising option for the patient at this time. Due to her orphan disease status, limited treatment options and favorable outcome and higher quality of life afforded with this treatment, you are requesting reconsideration of the denial. Anthem denied your request. Anthem says that the level of evidence is 2B (equivocal) in the current NCCN guidelines which is not sufficient to warrant medical necessity.

Anthem must follow Medicare rules. Medicare rules say that if there are no specific coverage rules for an item or service, then that item or service will be covered when it is medically necessary.

Our MAXIMUS Doctor Consultant says that the NovoTTF 100-A system is medically necessary for . We looked at this doctor's review, the file and Medicare rules. Based on this information, we decided that Medicare rules for coverage of the NovoTTF 100-A system have been met. Therefore, we decided that Anthem has to pre-approve the NovoTTF 100-A system (electrical field therapy) for .

If Anthem does not agree with our decision, they can ask us to open a case again. We only open a case again if we believe there was a mistake or if there is new information to review. The health plan has to show us the mistake and/or send us the new information. This does not happen often. If we decide to open the case again, we will send you a letter.



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novocure

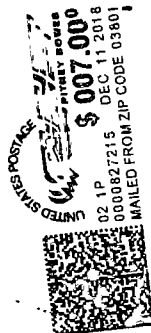
Novocure Inc.
195 Commerce Way
Portsmouth, NH 03801

TO:

C2C Solutions, Inc.
A Medicare Contractor
P O Box 44163
Jacksonville, FL 32231-4163

Received
C2C Mailroom
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Redetermination Case File Request/Transmittal DME QIC Form

COMPLETED BY QIC	1. Joint File Request Type		X QIC Request		Misfiled		Misrouted	
	<input type="checkbox"/> Supplemental File Request/Basis for Request							
	2. QIC Reconsideration #		1-8175102470		Reconsideration Request Date		December 17, 2018	
	3. AC Name / Number		CGS Administrators(17013)					
	4. Claim Type		<input type="checkbox"/> Part B <input checked="" type="checkbox"/> DME		Redetermination #		Multiple	
	4a. Overpayments		<input type="checkbox"/> RAC <input type="checkbox"/> PSC/ZPIC <input type="checkbox"/> AC/MAC MR Probe <input type="checkbox"/> Overpayment-other					
	5. * Beneficiary Name		Bene HIC#		Provider #		Redet. Date	
	Multiple		Multiple		Multiple		Multiple	
Claim # or CPT/HCPCS Codes at issue:		Multiple						
* Use Redetermination Request Continuation Sheet for multiple beneficiaries								
COMPLETED BY AC	AC Acknowledgement: Return to Name and QIC Fax #		LaCon Williams					
	AC Receipt Date & Signature							
	Exhibits List: Label exhibits with the letters provided below, and place them in order by letter. Refer to Exhibit List Quick Guide in JOA for detailed description of exhibits.							
	Procedural Documents		<input type="checkbox"/> A. Claims and System Screens <input type="checkbox"/> B. MSN or RA <input checked="" type="checkbox"/> C. Redetermination Request				<input checked="" type="checkbox"/> D. Redetermination Notice <input type="checkbox"/> E. Appointment of Rep. <input type="checkbox"/> F. Other	
	Evidentiary Documents		<input checked="" type="checkbox"/> G. Medical Records <input type="checkbox"/> H. Referral to/from Contractor Med. Staff <input type="checkbox"/> I. Contractor Medical Policies <input type="checkbox"/> L. Other				<input checked="" type="checkbox"/> J. Regs/CMS Rulings/NCDs, etc. <input type="checkbox"/> K. Overpayment Extrapolation Materials	
	Comments (discrepancies, no redetermination, other comments): <input type="checkbox"/> No redetermination <input type="checkbox"/> Claim fully paid <input type="checkbox"/> Incorrect HICN <input type="checkbox"/> Other _____ <input type="checkbox"/> Complete case previously sent to _____ (QIC) on (date) _____. No additional appellant information. <input type="checkbox"/> RAC <input type="checkbox"/> PSC/ZPIC <input type="checkbox"/> AC/MAC MR Probe <input type="checkbox"/> Overpayment <input type="checkbox"/> CERT							
	Interest in ALJ Participation: <input type="checkbox"/> Yes <input type="checkbox"/> No Position Paper Enclosed: <input type="checkbox"/> Yes <input type="checkbox"/> No							
	Form Completed By							
Name of Contact Person				Contact Phone #				
Date Sent				# of Boxes				
QIC Acknowledgement – AC Fax #								
QIC Receipt Date & Signature								

Redetermination Request Section 5

QIC Recon #	Beneficiary Name	Claim #	CPT/HCPCS	Dates of Service	Redeter Date	AC Redeter #
	HIC					
1-8175102470	Anniken S. Prosser 389044857A	18045802101000	E0766	01/16/2018	07/10/18	18157000135
1-8175102470	Anniken S. Prosser 389044857A	18050808224000	E0766	02/16/2018	07/10/18	18157000135
1-8175102470	Anniken S. Prosser 389044857A	18078813409000	E0766	03/16/2018	07/10/18	18157000135
1-8175102470	Anniken S. Prosser 389044857A	18107803853000	E0766	04/16/2018	07/10/18	18157000135

A

CLAIM FORMS

B

**MSN/RA
(if applicable)**

C

AC

REDETERMINATION

REQUEST

MEDICARE DME Redetermination Request Form

Supplier Information

Supplier Name Novocure INC

PTAN 6723630001 NPI 1255617569

Tax ID 205063536

Address 195 Commerce Way

City Portsmouth

State NH Zip Code 03801

Phone Number (603) 617-4768

☐ Jurisdiction A - Noridian Healthcare Solutions

☒ Jurisdiction B - CGS

☐ Jurisdiction C - CGS

☐ Jurisdiction D - Noridian Healthcare Solutions

Beneficiary Information

Patient Name Anniken S. Prosser

Medicare Number 389044857A

State Wisconsin

Phone Number (920)257-3574

Requestor's Name/Supplier Contact Name Sandy Rice

Requestor's Signature (required)

Sandy Rice

Date

06-05-2018

Overpayment Appeal ☐ Yes If yes, who requested overpayment: ☐ Medical Review ☐ ZPIC/PSC
☐ CERT ☐ Recovery Auditor

Date of Service	HCPCS & Modifiers	CCN	Date of Initial Determination
01/16/2018	E0766 KF RR	18045802101000	02/20/2018
02/16/2018	E0766 KF RR	18050808224000	02/23/2018
03/16/2018	E0766 KF RR	18078813409000	03/23/2018
04/16/2018	E0766 KF RR	18107803853000	04/23/2018

Suggested Documentation Check List: ☒ Medicare Remittance Advice ☒ CMN/DIF/Physician's Written Order
☐ ABN ☒ Medical Documentation

Reasons/Rationale - The submission of this redetermination is in regards to the denial code received: (CO-50)-"These are non-covered services because this is not deemed a 'medical necessity' by the payer." Novocure has been FDA approved since April 2011. Please see attached documentation for review.

Fax Numbers

Noridian Healthcare Solutions - JA 1-701-277-7865
CGS Administrators, LLC - JB 1-615-680-5976
CGS Administrators, LLC - JC 1-615-782-4630
Noridian Healthcare Solutions - JD 1-701-277-7886



Page 1 of 1
April 12, 2016.
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D

**AC
REDETERMINATION
NOTICE**

MEDICARE DME



July 10, 2018

Anniken Prosser
W2973 Farmstead Drive
Appleton, WI 54915-8120

Attention:

Enclosed is a copy of a letter we recently sent to the addressee named. If you have any questions about this letter, please contact us. If you are a Medicare beneficiary or representative, please call 1-800-Medicare (1-800-633-4227). If you are a supplier, please call 1-866-590-6727.

Sincerely

Medicare Administration

July 10, 2018

Novocure Inc
195 Commerce Way
Portsmouth, NH 03801-9999

Beneficiary Name: Anniken S. Prosser
HICN: XXX-XX-4857A
Appeal Number: 18157000135
Date of Service: January 16, 2018 through April 16, 2018
Type of Service: Tumor Treatment Field Therapy (TTFT)
Supplier: Novocure Inc

Dear Novocure Inc:

Please note that if you did not request this appeal, you are receiving this letter as a copy.

DECISION

This letter is to inform you of an **UNFAVORABLE** Medicare Appeal decision. Based on a new and independent review of the claims at issue, we find the electrical stimulation device is not covered by Medicare. The beneficiary is not responsible for payment. If you disagree with this decision, you may appeal to the Qualified Independent Contractor (QIC), C2C Innovative Solutions, Inc., as explained in the Future Appeal Rights section of this letter.

SUMMARY OF FACTS

Claims were submitted for the electrical stimulation device for dates of service January 16, 2018 through April 16, 2018. The claims were initially denied on February 20, 2018, because Medicare guidelines were not met. A redetermination request was received on June 6, 2018. The redetermination case included the following documentation: medical and administrative records.

APPLICABLE MEDICARE GUIDELINES AND RULES

The Medicare coverage policies are set forth below for the item or service in question. These rules are available at www.cgsmedicare.com.

- CMS Medicare Coverage Database, Local Coverage Determination (LCD) L34823-Tumor Treatment Field Therapy (TTFT)
- Social Security Act, Section 1879, Limitation on Liability

EXPLANATION OF DECISION

18157000135

The CMS Medicare Coverage Database, Local Coverage Determination (LCD) L34823-Tumor Treatment Field Therapy (TTFT) states that for any item to be covered by Medicare the items or services must: 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. It is expected that the beneficiary's medical records will reflect the need for the care provided. The beneficiary's medical records include the physician's office records, hospital records, nursing home records, home health agency records, records from other healthcare professionals and test reports. This documentation must be available upon request. Our review finds the following criteria have not been met:

- Tumor treatment field therapy (E0766) or therapy supplies (A4555) is not covered by Medicare as the currently published studies in the medical literature do not clearly document the effectiveness of this device. (LCD L34823- Tumor Treatment Field Therapy (TTFT), Coverage Indications, Limitations, and/or Medical Necessity)

A review of the documentation submitted with the redetermination request has been completed. Due to the Medicare guidelines discussed above, a favorable decision cannot be made at this time.

WHO IS RESPONSIBLE FOR THE BILL

After determining that the item or service will not be covered by Medicare, we must determine who is financially liable for the denied item or service. When an item or service is denied under §1862(a)(1), §1862(a)(9), or §1879(g) of the Social Security Act (the Act), we must determine if the beneficiary and the provider or supplier either knew or could reasonably be expected to know that the item or service would not be covered. This is known as the limitation on liability provision of §1879 of the Act.

If the beneficiary was informed by their provider or supplier in writing in advance of receiving the item/service that Medicare may not make payment (through receipt of an Advance Beneficiary Notice of Noncoverage (ABN)), the beneficiary may be responsible for the cost of the denied item or service. If the provider or supplier knew or could reasonably be expected to know the item or service would not be covered, but the beneficiary did not have such knowledge, then the provider or supplier may be responsible for the cost of the denied item or service.

In addition, we have determined that the supplier either knew or could reasonably be expected to know that the service/item would not be covered. After reviewing the claims, we have determined that the services were not reasonable and necessary. We have also determined the beneficiary could not have been expected to know these services were non-covered. Prior to furnishing this service you did not obtain a valid signed Advance Beneficiary Notice of Noncoverage notifying the beneficiary that Medicare may not pay. Based on the information contained in the CMS Medicare Coverage Database, Local Coverage Determination (LCD) L34823-Tumor Treatment Field Therapy (TTFT), you could have been expected to know these services were non-covered. Therefore, you are liable for full charges for the services.

You may not bill the beneficiary for the cost of the denied item or service, and must refund any monies collected from the beneficiary.

Beneficiaries who have incurred a charge for this service may be due a refund. In order to receive reimbursement, the beneficiary must submit the following to this office: (1) a copy of this notice,

(2) the supplier's invoice, and (3) a receipt or other documents indicating the beneficiary has made payment.

FUTURE APPEALS RIGHTS

If you disagree with this decision, you must request a reconsideration, in writing, within 180 days of receiving this letter. Your reconsideration request must include a copy of this letter along with the beneficiary's name, Medicare number, item or service in question, date of service, name of person appealing, signature, and date of signature. You may request an appeal by using the form enclosed with this letter. A copy of the reconsideration request form is also located at www.cgsmedicare.com or at www.C2Cinc.com. Reconsideration requests must be mailed to:

C2C Solutions, Inc.
Attn: DME Qualified Independent Contractor (QIC)
P. O. Box 44013
Jacksonville, FL 32231-4013

All evidence should be submitted with the reconsideration request. As explained in the Explanation of Decision section above, your reconsideration request should include documentation to support payment for the item billed. All evidence must be presented before the reconsideration decision is issued. You will not be allowed to submit any new evidence to the Administrative Law Judge or the Medicare Appeals Council unless you can demonstrate good cause for not submitting the evidence to the QIC during the reconsideration process.

NOTE: You do not need to resubmit documentation that was submitted as part of the redetermination. This information will be forwarded to the QIC as part of the case file utilized in the reconsideration process.

If you need more information or have any questions, please visit our Web site at www.cgsmedicare.com or call 1-866-590-6727.

Sincerely,

CGS, DME MAC Jurisdiction B
Medicare Appeals Department

cc: Anniken S. Prosser



RECONSIDERATION REQUEST FORM Redetermination Number: 18157000135
Contractor #: 17013, CGS, DME MAC Jurisdiction B

Directions: If you wish to appeal this decision, please fill out the information below and mail this form to the address below. At a minimum, you must complete/include information for items 1, 2a, 6, 7, 11, & 12, but to help us serve you better, please include a copy of the redetermination notice with your request.

C2C Solutions, Inc.
Attn: DME Qualified Independent Contractor (QIC)
P. O. Box 44013
Jacksonville, FL 32231-4013

1. Name of Beneficiary: _____
- 2a. Medicare Number: _____
- 2b. Claim Number (ICN/DCN, if available): _____
3. Provider/Supplier Name and Number (PTAN): _____
4. Person Appealing ☐ Beneficiary ☐ Provider ☐ Representative of Service
5. Address of the Person Appealing: _____
- 5a. Telephone Number of the Person Appealing: _____
- 5b. Email Address of the Person Appealing: _____
6. Item or service you wish to appeal: _____
7. Date of Service: From _____ To _____
8. Does this appeal involve an overpayment? ☐ Yes ☐ No
**Please include a copy of the demand letter with your request.*
9. Why do you disagree? Or what are your reasons for your appeal? (Attach additional pages, if necessary.) _____

10. You may also include any supporting material to assist your appeal. Examples of supporting materials include:
☐ Medical Records ☐ Office Records/Progress Notes ☐ Copy of the Claim
☐ Treatment Plan ☐ Certificate of Medical Necessity
11. Printed Name of Person Appealing: _____
12. Signature of Person Appealing: _____

Date: _____

Contractor Number: 17013, CGS, DME MAC Jurisdiction B



000560
0004 of 0004

E

APPOINTMENT OF REPRESENTATIVE

F

PSC, RAC, Overpayment

G

MEDICAL/ Administrative RECORDS

Change Healthcare		EFT/Check #:	09180510044	EFT/Check Date:	02/20/2018	EFT/Check Amount:	\$.00	Payment Type:	NON						
		Payer Name:		CGS - DME MAC JURISDICTION B		CH Payer Id:	MR031	CH Process Date:		02/21/2018					
		Provider Name:	NOVOCURE INC	Tax Id:	205063536	NPI:	1255617569	Other Payee Id:							
		Address:		185 COMMERCE WAY, PORTSMOUTH NH 038019989		Addl. Payee Id:	1255617569	Total PLB Adj Amt:		21000					
ERA Check 1 of 1															
Service Dates:		01/16/2018													
Processing Status:		4 - Denied													
Payer Claim # / Medicare ICN #:		18045802101000		CH Claim Trace Id:		044209776763659		Place Of Service:		Total Adjustment Amount:	\$.00				
Charge:		\$ 21,000.00		Paid:		\$.00		Patient Responsibility:		\$ -	Deductible:	\$ -			
Co-Insurance:		\$ -		Co-Pay:		\$ -		Other/Crossover Insurance:							
Remark Codes:	MA13	Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07)													
	MA01	Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/06, 4/1/07)													
	M26	The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10)													
	N115	This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/mcd, or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10)													
PATIENT - SUBSCRIBER INFORMATION															
Patient Name:				PROSSER, ANNIKEN S				Patient Id:		389044857A		Patient Control Number:		0001012478	
Corrected Patient/Subscriber Name:															
Subscriber Name:				Subscriber Id:				Group/Policy Id:							
Other Subscr. Name:				Other Subscriber Id:				Group/Policy Id:							
REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL															
Svc Line #	Service Date	Proc Code - Units	Charge \$	Allowed \$	Not Allowed \$	Deductible \$	Co-Ins \$	Co-Pay \$	Late Filing Red. \$	Paid \$					
1	01/16/2018	E0768 - 0 KF, RR	21,000.00	.00	.00	-	-	-	-	-					
SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES															
Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount \$									
1	3	CO	Contractual Obligations	50	These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present. Start: 01/01/1995 Last Modified: 07/01/2017	21,000.00									
Claim 1 of 1						Page 1 of 1									

Change Healthcare		EFT/Check #:	09180540034	EFT/Check Date:	02/23/2018	EFT/Check Amount:	\$.00	Payment Type:	NON	
		Payer Name: CGS - DME MAC JURISDICTION B		CH Payer Id: MR031		CH Process Date: 02/26/2018				
		Provider Name: NOVOCURE INC	Tax Id: 205063536	NPI: 1255617569		Other Payee Id:				
		Address: 185 COMMERCE WAY, PORTSMOUTH NH 038019999		Addl. Payee Id: 1255617569		Total PLB Adj Amt: 21000				
ERA Check 1 of 1										
Service Dates: 02/16/2018		Processing Status: 4 - Denied								
Payer Claim # / Medicare ICN #: 18050808224000		CH Claim Trace Id: 047211576398656		Place Of Service:		Total Adjustment Amount: \$.00				
Charge: \$ 21,000.00		Paid: \$.00		Patient Responsibility: \$ -		Deductible: \$ -				
Co-Insurance: \$ -		Co-Pay: \$ -		Other/Crossover Insurance:						
Remark Codes:	MA13	Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07)								
	MA01	Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07)								
	M25	The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 Last Modified: 11/01/2010 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10)								
	N115	This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/mcd, or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10)								
PATIENT - SUBSCRIBER INFORMATION										
Patient Name: PROSSER, ANNIKEN S			Patient Id: 389044857A			Patient Control Number: 0001012479				
Corrected Patient/Subscriber Name:										
Subscriber Name:			Subscriber Id:			Group/Policy Id:				
Other Subscr. Name:			Other Subscriber Id:			Group/Policy Id:				
REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL										
Svc Line #	Service Date	Proc Code - Units Modifiers	Charge \$	Allowed \$	Not Allowed \$	Deductible \$	Co-Ins \$	Co-Pay \$	Late Filing Red. \$	Paid \$
1	02/16/2018	E0766 - 0 KF, RR	21,000.00	.00	.00	-	-	-	-	-
SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES										
Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount \$				
1	3	CO	Contractual Obligations	50	These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present. Start: 01/01/1995 Last Modified: 07/01/2017	21,000.00				
Claim 1 of 1					Page 1 of 1					

Change Healthcare ERA Check 1 of 1		EFT/Check #: 09180820023	EFT/Check Date: 03/23/2018	EFT/Check Amount: \$.00	Payment Type: NON					
		Payer Name: CGS - DME MAC JURISDICTION B		CH Payer Id: MR031	CH Process Date: 03/26/2018					
		Provider Name: NOVOCURE INC	Tax Id: 205063536	NPI: 1255617569	Other Payee Id:					
		Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999		Addl. Payee Id: 1255617569	Total PLB Adj Amt: 21000					
Service Dates: 03/16/2018		Processing Status: 4 - Denied								
Payer Claim # / Medicare ICN #: 18078813409000		CH Claim Trace Id: 075224952936657	Place Of Service:	Total Adjustment Amount: \$.00						
Charge: \$ 21,000.00		Paid: \$.00	Patient Responsibility: \$ -	Deductible: \$ -						
Co-Insurance: \$ -		Co-Pay: \$ -	Other/Crossover Insurance:							
Remark Codes:	MA13	Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07)								
	MA01	Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07)								
	M25	The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10)								
	N115	This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/mcd, or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10)								
PATIENT - SUBSCRIBER INFORMATION										
Patient Name: PROSSER, ANNIKEN S		Patient Id: 389044857A		Patient Control Number: 0001012479						
Corrected Patient/Subscriber Name:										
Subscriber Name:		Subscriber Id:		Group/Policy Id:						
Other Subscr. Name:		Other Subscriber Id:		Group/Policy Id:						
REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL										
Svc Line #	Service Date	Proc Code - Units Modifiers	Charge \$	Allowed \$	Not Allowed \$	Deductible \$	Co-Ins \$	Co-Pay \$	Late Filing Red. \$	Paid \$
1	03/16/2018	E0766 - 0 KF, RR	21,000.00	.00	.00	-	-	-	-	-
SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES										
Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount \$				
1	3	CO	Contractual Obligations	50	These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present. Start: 01/01/1995 Last Modified: 07/01/2017	21,000.00				
Claim 1 of 1			Page 1 of 1							

Change Healthcare ERA Check 1 of 1		EFT/Check #: 09181130049	EFT/Check Date: 04/23/2018	EFT/Check Amount: \$.00	Payment Type: NON					
		Payer Name: CGS - DME MAC JURISDICTION B		CH Payer Id: MR031	CH Process Date: 04/24/2018					
		Provider Name: NOVOCURE INC	Tax Id: 205063536	NPI: 1255617569	Other Payee Id:					
		Address: 195 COMMERCE WAY, PORTSMOUTH NH 038019999		Addl. Payee Id: 1255617569	Total PLB Adj Amt: 21000					
Service Dates: 04/16/2018		Processing Status: 4 - Denied								
Payer Claim # / Medicare ICN #: 18107803853000		CH Claim Trace Id: 106238980798659	Place Of Service:	Total Adjustment Amount: \$.00						
Charge: \$ 21,000.00		Paid: \$.00	Patient Responsibility: \$ -	Deductible: \$ -						
Co-Insurance: \$ -		Co-Pay: \$ -	Other/Crossover Insurance:							
Remark Codes:	N793	Alert: CMS is changing from the Medicare Health Insurance Claim number (HICN) to the new Medicare Beneficiary Identifier (MBI). You can use either the HICN or MBI during the transition period. Visit www.cms.gov/newcard for important dates and information about this change. Start: 07/01/2017 Last Modified: 11/01/2017 Notes: (Modified 11/1/2017)								
	MA13	Alert: You may be subject to penalties if you bill the patient for amounts not reported with the PR (patient responsibility) group code. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 4/1/07)								
	MA01	Alert: If you do not agree with what we approved for these services, you may appeal our decision. To make sure that we are fair to you, we require another individual that did not process your initial claim to conduct the appeal. However, in order to be eligible for an appeal, you must write to us within 120 days of the date you received this notice, unless you have a good reason for being late. Start: 01/01/1997 Last Modified: 04/01/2007 Notes: (Modified 10/31/02, 6/30/03, 8/1/05, 4/1/07)								
	M25	The information furnished does not substantiate the need for this level of service. If you believe the service should have been fully covered as billed, or if you did not know and could not reasonably have been expected to know that we would not pay for this level of service, or if you notified the patient in writing in advance that we would not pay for this level of service and he/she agreed in writing to pay, ask us to review your claim within 120 days of the date of this notice. If you do not request an appeal, we will, upon application from the patient, reimburse him/her for the amount you have collected from him/her in excess of any deductible and coinsurance amounts. We will recover the reimbursement from you as an overpayment. Start: 01/01/1997 Last Modified: 11/01/2010 Notes: (Modified 10/1/02, 6/30/03, 8/1/05, 11/5/07, 11/1/10)								
	N115	This decision was based on a Local Coverage Determination (LCD). An LCD provides a guide to assist in determining whether a particular item or service is covered. A copy of this policy is available at www.cms.gov/mcd , or if you do not have web access, you may contact the contractor to request a copy of the LCD. Start: 05/30/2002 Last Modified: 07/01/2010 Notes: (Modified 4/1/04, 7/1/10)								
PATIENT - SUBSCRIBER INFORMATION										
Patient Name: PROSSER, ANNIKEN S		Patient Id: 389044857A		Patient Control Number: 0001012479						
Corrected Patient/Subscriber Name:										
Subscriber Name:		Subscriber Id:		Group/Policy Id:						
Other Subscr. Name:		Other Subscriber Id:		Group/Policy Id:						
REMITTANCE PROCESSING INFORMATION - SERVICE LINE DETAIL										
Svc Line #	Service Date	Proc Code - Units Modifiers	Charge \$	Allowed \$	Not Allowed \$	Deductible \$	Co-Ins \$	Co-Pay \$	Late Filing Red. \$	Paid \$
1	04/16/2018	E0766 - 0 KF, RR	21,000.00	.00	.00	-	-	-	-	-
SUPPLEMENTAL INFORMATION/ADJUSTMENT INFORMATION - SERVICE LINES										
Svc Line #	Core Business Scenario	Supp/Adj Group Code	Description	Supp/Adj Reason Code	Description	Amount \$				
1	3	CO	Contractual Obligations	50	These are non-covered services because this is not deemed a 'medical necessity' by the payer. Usage: Refer	21,000.00				

Anniken S. Prosser
W2973 Farmstead Dr.
Appleton, WI 54915

October 24, 2017

Attn: Medicare Appeals
Re: Denial of My Cancer Treatment
Policy#: 389-04-4857-A

To whom it may concern:

This letter is in response to Medicare's denial of my physician's prior authorization request for coverage of Tumor Treatment Fields therapy (TTF) using Optune for my glioblastoma.

I am submitting this letter as an urgent member grievance so that I may obtain approval of my badly needed, FDA APPROVED, treatment for my cancer.

According to the letter we received from Medicare, the request for coverage for services was denied based upon the following reason: experimental.

First of all, I have to strongly disagree with this rationale. This treatment has been approved by the **United States Food and Drug Administration** for treatment of recurrent glioblastoma. Furthermore, my physician feels that this treatment is my best hope for slowing down the progression of my disease. I find it unconscionable that Medicare is second guessing the treatment decisions of my physician, Dr. Jennifer Connelly, who is one of the country's leading experts on this treatment.

TTF is my **best option** to treat this fatal disease. I have submitted the attached clinical information from my physicians as well as peer reviewed literature to assist you in considering approval of this treatment.

This procedure has been covered by many local and national insurance companies including: Medicare, Aetna (**Medical Policy Bulletin 0827**), Humana, Health Net (**Medical Policy Bulletin NMP523**), Health Partners (**Medical Policy Bulletin E003-01**), United Healthcare, Cigna (HMO and PPO), Anthem Blue Cross Blue Shield, BCBS Texas/Illinois/New Mexico/Oklahoma, Blue Cross Blue shield of Louisiana, Blue Cross Blue Shield of Michigan, HealthLink, Kaiser Permanente, Harvard Pilgrim Health Care, GHI, Horizon Blue Cross Blue Shield of New Jersey, NYS Empire Plan, Network Health Plan, and Blue Cross Blue Shield of Florida. This is only a representative sampling of payers covering Optune for this cancer indicating that there is enough "proven" evidence to warrant coverage for Optune in treating glioblastoma. **I am demanding that my clinical situation be reviewed by a board certified physician specializing in neuro-**

oncology or neurosurgery who has specific expertise in treating patients with glioblastoma with TTF.

I am a 34 year old woman with glioblastoma. I like drawing, writing lyrics and singing for the bands Antidote For Sorrow and Resisting the Solace. I also enjoy spending time with family and friends. I married Barry Prosser in September 2010. We have a son, Liam; he will be 4 years old on January 31st. I am currently not working. I enjoy vacations at the cottage.

I was diagnosed at the ER in February 2016. I had surgery at St. Elizabeth Hospital in Appleton Wisconsin and it was confirmed that I had GBM. I have had the following treatments; surgery, radiation, chemotherapy and Optune. I am off chemotherapy now, possibly may have to do more in the future still on Optune. I experienced the following symptoms; passing out, bad headaches, dizziness, throwing up, but these have been better with treatments and Optune. I have had fewer side effects with Optune and it is helping me so much. I am able to get up each day and be with my husband and son because of Optune. In my own words, I believe Optune is helping me very much; I am smiling because it's helping me keep the pain away!

After discussing treatment options with Dr. Jennifer Connelly, my doctor decided to prescribe Optune. Given the aggressive nature, and extremely limited treatment options of my disease, my doctor recommended I receive coverage for Optune, as it is the best FDA approved option at this time for treating my glioblastoma. I began utilizing TTFields on June 16, 2016.

Alternating electric field therapy (Optune) + adjuvant temozolomide is now an NCCN Category 2A recommendation following postoperative standard brain radiation therapy with concurrent temozolomide.


I am aware that my cancer is considered an "orphan disease," by the National Institutes of Health due to the rarity of people who get glioblastoma. Despite these interventions I have received to date, TTF therapy is my best hope to control my brain tumor.

I cannot emphasize enough the urgency and importance of this matter.

Should you have any additional questions regarding my condition or the proposed treatment, please feel free to contact me at (920)-257-3574.

I also give consent for Novocure to work on the appeal on my behalf.

Thank you for your timely consideration and hopeful approval of this case.

Sincerely, 

Anniken S. Prosser

Attachments

04-13-'18 17:59 FROM-

T-200 P0004/0006 F-801

★OPTUNE

Optune® Prescription Form

Please fax or email signed and completed forms with medical records, face sheet, and copies of insurance card(s) to 603-501-4298 or support@novocure.com

I. PRESCRIPTION INFORMATIONPatient Name: Anniken Prosser

(required)

Date of Birth: 10/10/03

(required)

Please check the appropriate box:

☐

New Patient order

☒

Renewal

Is this patient enrolling in an Investigator Sponsored Trial (IST) or Cooperative Group Trial (e.g. RTOG)?

☐

Yes

If yes, which trial? _____

Optune is comprised of: an Electric Field Generator (the "Device"), Transducer Arrays (the "Arrays"), power supply items, and accessories.

ICD-10 Code: C71.9

(required)

Diagnosis Description: Glioblastoma Multiforme

I prescribe use of Optune, as described above, for a period of:

(check box required)

☐

3 months

☒

6 months

Prescriber Information:

Prescriber Name (Last, First, Middle Initial): Connolly Jennifer M.

(required)

Name of Preferred Office Contact: Carrie GuzleckiNPI: 1700768531

(required)

Phone: 414-805-5231Phone: 414-805-5204

(required)

Fax: 414-259-0469

(required)

Email: carrie.guzlecki@freednet.com

(required)

By signing and dating, I attest that I am prescribing Optune (DO NOT SUBSTITUTE) as medically necessary. I have read and understand all safety information and other instructions for use included with Optune.

Prescriber Signature: [Signature]

(required)

Date: 04/13/2018

(required)

II. ORDER INFORMATION

Treatment education, head preparation and array application will take place in the patient's home. Upon completion of the education session, the patient or caregiver may initiate treatment in the presence of Novocure personnel.

Preferred Treatment Start date (MM/DD/YYYY): _____

Please allow 5 business days from submission of all required paperwork and preferred treatment start date.

Notes: Continuation of treatment

10-17-'17 17:45 FROM-

T-084 P0002/0004 F-636



Optune® Prescription Form

Please fax or email signed and completed forms with medical records, face sheet, and copies of insurance card(s) to 603-501-4298 or support@novocure.com

I. PRESCRIPTION INFORMATION

Patient Name: <u>Annika Prosser</u> <small>(required)</small>		Please check the appropriate box: <input type="checkbox"/> New Patient order	
Date of Birth: <u>10/10/83</u> <small>(required)</small>		<input checked="" type="checkbox"/> Renewal	
Is this patient enrolling in an Investigator Sponsored Trial (IST) or Cooperative Group Trial (e.g. RTOG)? <input type="checkbox"/> Yes If yes, which trial? _____			
Prescription Information Optune is comprised of: an Electric Field Generator (the "Device"), Transducer Arrays (the "Arrays"), power supply items, and accessories.			
ICD-10 Code: <u>C71.9</u> <small>(required)</small>		Diagnosis Description: <u>Glioblastoma MultiForme</u>	
I prescribe use of Optune, as described above, for a period of: <small>(check box required)</small>		<input type="checkbox"/> 3 months <input checked="" type="checkbox"/> 6 months	
Prescriber Information <u>Connelly Jennifer M</u> Prescriber Name (Last, First, Middle Initial): <small>(required)</small>		Contact Information <u>Carrie Guzacki</u> Name of Preferred Office Contact	
NPI: <u>1780768531</u> <small>(required)</small>		<u>414-805-5231</u> Phone	
<u>414-805-5204</u> Phone		<u>414-259-0469</u> Fax	
		<u>carrie.guzacki@freedom.com</u> Email	
Signature Required By signing and dating, I attest that I am prescribing Optune (DO NOT SUBSTITUTE) as medically necessary. I have read and understand all safety information and other instructions for use included with Optune.			
Prescriber Signature: <u>[Signature]</u> <small>(required)</small>		Date (MM/DD/YYYY): <u>10/17/2017</u> <small>(required)</small>	

II. ORDER INFORMATION

Treatment education, head preparation and array application will take place in the patient's home. Upon completion of the education session, the patient or caregiver may initiate treatment in the presence of Novocure personnel.

Preferred Treatment Start date (MM/DD/YYYY): _____

Please allow **5 business days** from submission of all required paperwork and preferred treatment start date.

Notes <u>Continuation</u>



Optune™ Prescription Form

Fax the completed form with signature to 603-501-4298; or Email to support@novocure.com

III. PATIENT INFORMATION (PLEASE COMPLETE IN FULL)

Patient Information			
Permanent Address: <u>Wd 973 Farmstead Dr.</u>			
City: <u>Appleton</u>	State: <u>WI</u>	Zip: <u>54915</u>	Phone: <u>920-257-3574</u>
Family Contact: <u>Barry Prosser</u>		Phone: _____	
<input checked="" type="checkbox"/> Shipping and mailing address same as permanent address.		<input type="checkbox"/> Use the address below for shipping and mailing purposes related to equipment, supplies and billing. Patient must reside at this address:	
Shipping and Mailing Address: _____			
City: _____	State: _____	Zip: _____	Phone: _____
Insurance Information			
Primary Insurance: <u>National POS - Humana</u>			
Patient ID#: <u>100303812</u>	Insurance Phone Number: <u>866-427-7478</u>		
Group#: <u>668526</u>	Group Name: _____		
Primary Insured (Subscriber) Name: <u>Barry Prosser</u>			
Relationship to Patient: <u>Husband</u>	Subscriber Date of Birth: <u>5/24/85</u>		
**If you have secondary insurance, please attach this information if applicable.			

The use of "I" or "you" in this document refers to the patient named in the "Signatures" block.

Authorization to Release Records to Novocure

I authorize my physician and the practice, facility and hospital of my physician and any other holder of medical information about conditions for which I am being treated to release to Novocure Inc. and affiliated companies (together "Novocure") any information necessary for treatment, payment and healthcare operations related to my use of Optune. I authorize Novocure employees to deliver equipment and provide education in my home as well as attend my appointments as necessary to provide technical assistance to my physician and healthcare practitioners. I also authorize Novocure, my physician and the practice, facility and hospital of my physician and any other holder of medical information about conditions for which I am being treated to release such information to my insurer. These authorizations apply to my current physician and previous physicians. I understand that Novocure may and likely will use the information to seek a determination of whether my insurer will cover my use Optune.

Authorization To Discuss Care

I authorize Novocure to discuss my care with the family members and/or caregivers listed below. I may revoke this authorization at any time by calling or emailing Novocure at 855-281-9301 or support@novocure.com.

List all authorized individuals: Barry Prosser, Daniel Mass, Hilda Staven
 Signatures: Amber S. Prosser - ma

Patient Name (please print): Amber S. Prosser Date: 5-31-16

If anyone other than patient completes or signs this form, please enter the following information:

Name: _____ Telephone Number: _____
 Address: _____ City: _____
 State: _____ Zip: _____
 Relationship to Patient: _____ Reason for Signing: _____

06/14/2016 11:35 141 50352

HOPE

PAGE 02/13



Froedtert and the Medical College of Wisconsin Cancer Center
9200 W Wisconsin Ave
Milwaukee, WI 53226
414-805-6800

REVIEW OF DENIED TREATMENT REQUEST
Life Threatening Condition

June 14, 2016

Humana
Clinical Review Team
1100 Employers Boulevard
Green Bay, WI 54344

ATTN: Provider Appeal

RE: Anniken Prosser
Policy: 100303512
DOB: 10/10/1983

This letter is in response to the denial received after review of predetermination of benefits for my patient, Anniken Prosser. It is my understanding that Ms. Prosser is entitled to appeal this adverse benefit determination. Your denial letter indicates that you consider treatment with Optune to be investigational.

Please accept this letter as a formal appeal for coverage for Optune. I am also reiterating our request for a network exception for this patient due to the fact that there is no provider in the Humana network who can provide this service. I also request that a physician who is experienced in treating glioblastoma review this material as regulated by ERISA. The type of physician familiar with the treatment of glioblastoma would be a neuro-oncologist or radiation oncologist with specific expertise treating GBM.

Anniken Prosser is a young 32-year old female who initially presented with a severe migraine with associated nausea. MRI revealed a large enhancing left temporal cystic mass. She underwent a gross total resection on February 25, 2016. Pathology demonstrated glioblastoma multiforme. Following surgery, she went on to initiate treatment with radiation with concurrent Temodar. This was completed in May of 2016. After discussing treatment options with Ms. Prosser, I have decided to prescribe Optune in combination with temozolomide as this currently is the best option for treating her glioblastoma.

Optune is an innovative approach to cancer treatment, using tumor treating fields (TTFields) to interfere with the division of malignant cells. TTFields therapy is a locally or regionally delivered treatment that uses alternating electric fields to disrupt the rapid

Anniken S Prosser MR#: 10790724

06/14/2016 11:35 141- 30352

HOPE

PAGE 03/13

cell division exhibited by cancer cells. GBM patients treated with TTFields wear insulated transducer arrays on the scalp attached to the portable electric field generator.

Optune received pre-market approval from the FDA for recurrent glioblastoma in April 2011. This approval was based on the results of a large randomized controlled trial of patients with recurrent GBM comparing Optune as a monotherapy to standard chemotherapy used in recurrent GBM. The results showed that treatment with Optune delivered comparable overall survival and progression free survival to chemotherapy with minimal toxicity and an improvement in patients quality of life compared to chemotherapy.

In 2015, Optune received pre-market approval from the FDA for newly diagnosed glioblastoma in combination with temozolomide after standard surgical resection and radiation therapy. This approval was based on a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of newly diagnosed GBM patients treated with Optune and TMZ to those treated with TMZ alone. The results of the trial at the interim analysis showed superior efficacy both in progression free survival as well as overall survival. The data was so compelling that the independent data monitoring committee recommended the trial be terminated so that patients in the standard of care arm could cross over. The FDA approved the supplemental IDE to allow for crossover of patients on the control arm to the TTFields arm on December 1, 2014.

The pre-specified, interim analysis of EF-14 trial data was conducted on the first 315 patients, representing approximately 50 percent of the targeted study population. The data show that:

Patients treated with TTFields together with temozolomide demonstrated a significant increase in progression free survival compared to temozolomide alone (median PFS of 7.1 months compared to 4.0 months, respectively, hazard ratio=0.63, p=0.001).

Patients treated with TTFields together with temozolomide demonstrated a significant increase in overall survival compared to temozolomide alone (median OS of 19.6 months compared to 16.6 months, respectively, hazard ratio=0.75, p=0.034).

The percentage of patients alive at 2 years in the TTFields together with temozolomide arm was 43% compared to 29% in the temozolomide alone arm.

Glioblastoma is an orphan disease, with limited available treatment options. Most payers are covering Optune for patients based on published medical policy as well as individual medical necessity review. Over 180 payers including Humana, have covered this therapy for members after an appeal process. This new data is an important advancement in the treatment of glioblastoma. It is imperative that Humana review their current policy for Optune and amend it to cover this therapy for patients with glioblastoma.

At Froedtert Health and Medical College of Wisconsin, Optune has been employed successfully for patients such as Ms. Prosser, and we have achieved excellent outcomes. We have been very fortunate in working with payers who specifically consider the above information as well as the patient's orphan disease status in issuing

Anniken S Prosser MR#: 10790724

06/14/2016 11:35 141 30352

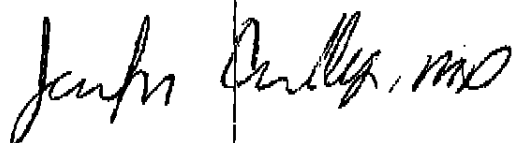
HOPE

PAGE 04/13

positive coverage for our patients. I request Humana, offer the same consideration to Ms. Prosser, when considering this request for coverage of Optune.

It is my belief that Optune in combination with temozolomide is the most appropriate option for her at the present time. Based upon her orphan disease status, limited treatment options and the recently published peer reviewed data showing superiority of adding Optune to temozolomide I respectfully request reconsideration of the adverse benefit determination.

Sincerely,



Jennifer Connelly, MD
Neurology
Neuro-Oncology - Board Certified
Froedtert Health and Medical College of Wisconsin
Phone: 414-805-5204
Fax: 414-805-5252

Annika S Prosser MR#: 10790724

Start + Care: 6/1/16
 70% alcohol (✓)
 shaved (✓)

ASSESSMENT of NEED

Customer Name: MS	Annika Prosser	Date:	6/8/16
Customer #	1012479		
DSS/Site	den Nancy Newberg / Fredrick + med cal	Initiation:	Home <input checked="" type="checkbox"/> Office <input type="checkbox"/>

Responsible Party/ Emergency Contact:		Tel:
Mr. Barry Prosser		920-257-4525 920-257-3574

Patient acknowledges that financial responsibility has been discussed and agreed to: (Indicate date of welcome call and person spoken to)	
Patti 6/7/16	

How did you hear about Optune Therapy? Physician			
What factors led to the decision to start treatment? Physician			
Did you receive a package from us containing printed material and DVD? Yes No Not Sure			
Does patient live alone? Yes No		Patient has access to telephone: Yes No	
Is patient residence? Home Assisted Living Other facility:			
In what type of structure do you reside? House - Apart/Condo - Assisting Living - Rehab Facility			
Where will parking be? Yes No Driveway			
How will we enter / exit residence? Front door, ring doorbell, 2 steps			
Should I be made aware of any safety concerns? ex lack of lighting, no elevator (if apt is not on 1 st floor)			
Please specify: N/A			
Are there any pets in your home? Yes No		Cats #	Dogs # 2 Other types #
Can pets be placed in another room while DSS present? Yes No N/A			
Is there smoking in the home? Yes No			
Is there anything that our DSS should know about the home environment or the people residing there that could be important for the safety of the visit? N/A			
Is patient able to speak: Yes No If yes, what is his/her primary language? English			
Does patient have adequate electrical capacity to utilize device and recharge batteries Yes No			
Does he/she require assistance with mobility? Yes No			
Are you employed? Yes No		If so do you plan on continuing to work? Yes No	
If you are planning on continuing to work what is your occupation? N/A			
Have you discussed treatment during work hours with your employer? Yes - (No)			

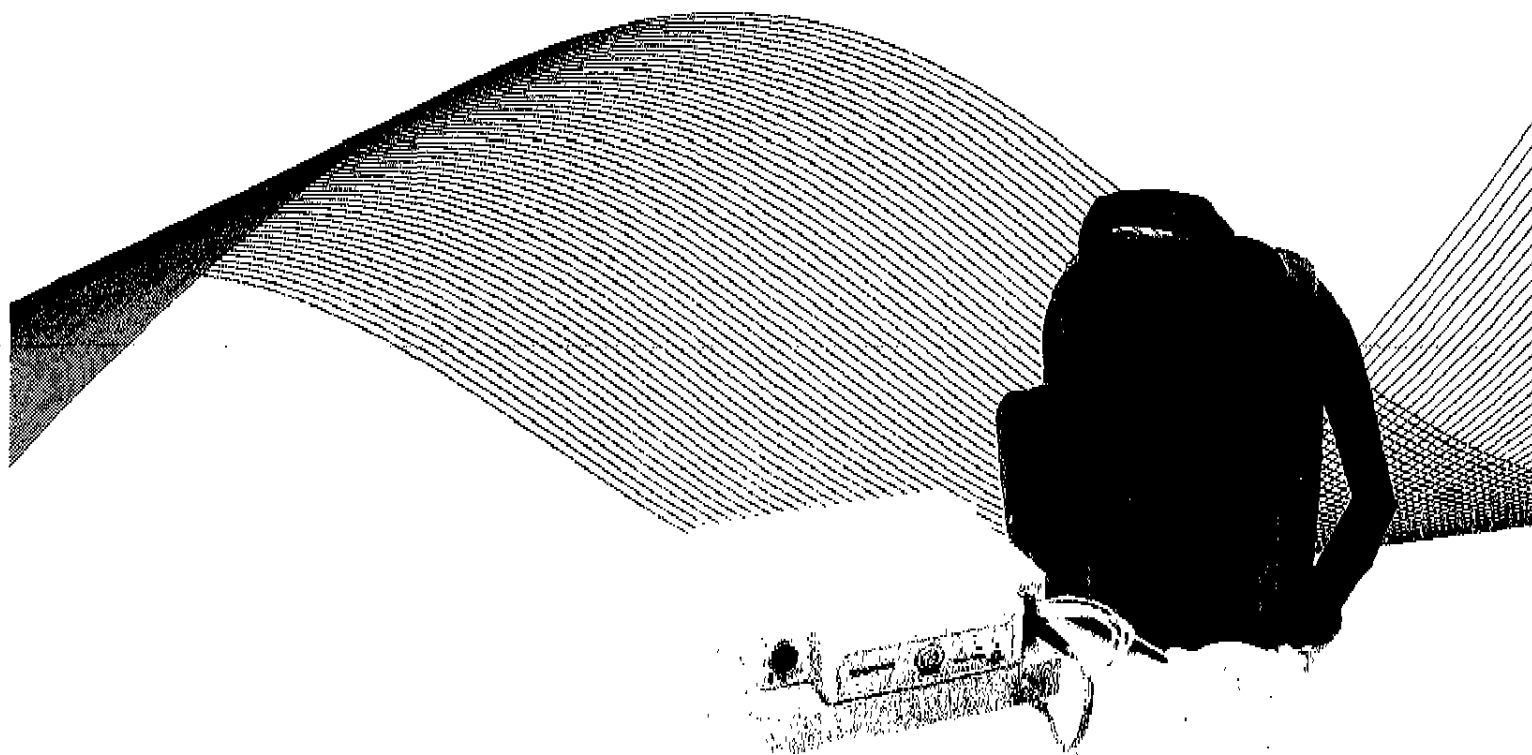
See Technical Review Checklist: Yes - No	
Other: (Explain)	
Explain any special needs or additional training required (if applicable) N/A	
Training on the Optune device is performed, conducted, and observed by certified physicians in accordance with FDA approval guidelines.	
Completed by:	Date: 6/8/16

ANNIKEN PROSSER #1012479

NovoTTF™-100A System is now



OPTUNE™
SERVICE AGREEMENT



novocure™

Printed on: 10 May 2016, 07:28:05 am; Printed by: BMILLS.

Case 1:20-cv-00194-WCG Filed 04/28/20 Page 293 of 539 Document 11-6 5155

Supply Terms For Optune™

Background

Novocure™ Inc. is referred to as "we" or "Novocure" in this service agreement ("Service Agreement"). The use of "you" or "your" refers to the patient named in the associated Service Agreement. All capitalized terms not defined herein have the meaning defined in the Service Agreement.

Supply Terms

Optune (the "System") is comprised of two main components: (1) an Electric Field Generator (the "Device"); and (2) INE Transducer Arrays (the "Arrays") that are disposable supplies to the Device. The System also consists of power supply items and accessories.

Novocure's affiliates hold patents that cover the System, various components of the System, and using the System. Novocure hereby grants an expressly conditional license to you to use the inventions covered by those patents under the terms set forth herein. No other licenses to you is implied.

As an element of consideration for the grant of a license to you, you agree to pay Novocure a monthly fee for access to the System. Notwithstanding anything to the contrary contained in this agreement, any use of the System for which this element of consideration is absent is not licensed under the patents.

You acknowledge that, taken together, the consideration due to Novocure for access to the System reflects only the value of the "use" rights conferred by Novocure, and does not provide you with the same suite of rights that would accompany an unconditional sale. Notwithstanding anything to the contrary contained in this agreement, (1) you are not

licensed to use the Device with Arrays that were not purchased from Novocure; and (2) you are not licensed to use any given Array for more than seven (7) days.

You understand that the Device shall at all times remain the property of Novocure.

You understand and agree that Novocure has the right to inspect the System upon request and that you may be responsible for the replacement value of the System in the event it is lost, damaged, or stolen while in your possession or control.

You understand that: (i) Novocure has the option to provide new or used equipment including the Device, power supplies and accessories; (ii) you shall not modify or alter any equipment provided to you by Novocure; (iii) you will notify Novocure immediately of any equipment problems; and (iv) the equipment is only to be used upon the order and direction of your doctor.

You understand that the System fees will continue until the date that you call Novocure to pick up the System. You understand that Novocure may stop providing the technical support for the System and may stop providing additional Arrays or replacement items if you fail to comply with the terms of the Service Agreement and Supply Terms, including failure to pay amounts owed or to remit payments due to Novocure that you receive directly from payers.

Patient Care Responsibilities

You understand and acknowledge that (1) your care is under the supervision and control of your treating physician or other healthcare provider (e.g., nurse practitioner, physician's assistant) who is appropriately licensed, trained and authorized to prescribe and administer the System, (2) your physician or other healthcare provider has prescribed the System as part of your treatment and has explained to you its risks, advantages, possible complications and

alternatives, and why it is considered necessary treatment for your condition, (3) Novocure's services do not include diagnostic, prescriptive or other functions pertaining to licensed physicians or healthcare providers, and (4) your physician or other healthcare provider is solely responsible for diagnosing and prescribing drugs, equipment and therapy for your condition and otherwise supervising and controlling your medical condition.

Financial Responsibilities

The rental fee for the System, including use of the Device, related power supplies/accessories and Arrays for 30 days is \$21,000.

Please call (855) 281-9301 if you have any questions about your financial responsibilities.

Novocure will review your insurance or third party payer (together "Payer") coverage for the purposes of providing you with an estimate of your out of pocket costs associated with the rental fee to use the Device and the purchase of Arrays. Novocure will also prequalify you for eligibility for our Patient Assistance Programs. Formal qualification for financial assistance will require a separate application and documentation of income.

Novocure will submit a claim to your Payer for the System and may appeal such claim if denied. Novocure will bill you for your financial responsibilities related to the System when i) your Payer affirms coverage for your use of the System at the list rental fees and supply prices for the System or ii) Novocure elects not to continue appeals of your case.

If your cost share for the System is not affordable or your Payer refuses to provide coverage for the System, you can also apply to Novocure for financial assistance

Please contact 855-281-9301 or email **support@novocure.com** to inquire about financial assistance programs.

Warranty Information

Novocure will provide a replacement Device in the event of malfunction that cannot be corrected over the phone by our technical support staff. Novocure will provide replacement Arrays in the event that the Transducer Arrays are defective to manufacturer standards. Novocure will provide replacement power supplies and accessories in accordance with the expected useful lifetime of these items. The above warranty is only valid if the System is used in accordance with the User Manual provided to you. This warranty is personal to you and non-transferable.

Lost equipment, including the Device, Arrays, power supplies and related accessories, and equipment damaged by you or your caregivers is not covered by this warranty.

Patient Information Form For Optune™

Background

Novocure™ Inc. is referred to as "Novocure" in this service agreement ("Service Agreement"). The use of "you" or "your" refers to the patient named in the associated Service Agreement. All capitalized terms not defined herein have the meaning defined in the Service Agreement.

Notice of Privacy Practices

THIS NOTICE DESCRIBES HOW HEALTH INFORMATION ABOUT YOU MAY BE USED AND DISCLOSED AND HOW YOU CAN GET ACCESS TO THIS INFORMATION. PLEASE REVIEW IT CAREFULLY.

Please contact 855-281-9301 or support@novocure.com if you have questions.

Purpose of this Notice

This notice will tell you about the ways in which Novocure may use and disclose your health information that identifies you ("PHI"). We also describe your rights and certain obligations we have regarding the use and disclosure of PHI.

Our Pledge Regarding Protected Health Information

We understand that health information about you and your health is personal. We are committed to protecting health information about you. We create a record of the products and services that we provide to you. We need this record to provide you with quality products and services used in your care and to comply with certain legal requirements. This notice applies to all of the PHI we use and disclose related to the products and services used in your care. Your personal doctor, healthcare provider and other entities

providing products or services to you may have different policies or notices regarding their use and disclosure of your PHI.

Our Legal Requirements

We are required by law to:

- Make sure that health information that identifies you is kept private;
- Give you this notice of our legal duties and privacy practices with respect to PHI about you;
- Notify you if we are unable to agree to a requested restriction on how your information is used and disclosed;
- Accommodate reasonable requests that you may make to communicate PHI by alternative means or at alternative locations;
- Obtain your written authorization for purposes other than those listed below and permitted under law; and
- Follow the terms of the notice that currently is in effect.

Who Will Follow Our Privacy Practices

This notice describes Novocure's practices and that of all Novocure employees, staff and other company personnel for US operations only.

These entities, sites and locations follow the terms of this notice. Additionally, these entities sites and location may share PHI with each for treatment, payment or health care operations purpose described in this notice.

Your Rights Regarding Protected Health Information About You

You have the following rights regarding PHI we maintain about you:

Right to Inspect and Copy

You have the right to inspect and copy PHI that may be used to make decisions about your care. Usually this includes medical and billing records. To inspect and copy PHI that may be used to make decisions about you, please contact 855-281-9301 or support@novocure.com. We may charge a fee for copying requested files. We may deny your request to inspect and copy in certain circumstances. If you are denied access to PHI, you may request that the denial be reviewed. Another person chosen by us will review your request and the denial. We will comply with the outcome of that review.

Right to Amend

If you feel that PHI we have about you is incorrect or incomplete, you may ask us to amend the information. You have the right to request an amendment for as long as the information is kept by us. To request an amendment, please contact 855-281-9301 or support@novocure.com. You must provide a reason that supports your request. We may deny your request for an amendment if it does not include a reason to support that request. Additionally, we may deny your request if you ask us to amend information that:

- Was not created by us, unless the person or entity that created the information is no longer available to make the amendment,
- Is not part of the PHI kept by or for us
- Is not part of the information which you would be permitted to inspect and copy; or
- Is accurate and complete.

Right to Accounting of Disclosures

You have the right to request an "accounting of disclosures". This accounting is a list of the disclosure we made of PHI about you. Novocure will provide an accounting of all but the following types of disclosure:

- Those made for treatment, payment and health care operations;
- Those made to you about your own PHI;
- Those made to persons involved in your care or other notification purposes;
- Those made pursuant to an authorization signed by you disclosing specific uses and disclosures;
- Where the disclosures are part of a Limited Data Set (as defined in the Health Insurance Portability and Accountability Act);
- Where the disclosures are incidental to an otherwise permissible disclosure;
- For national security or intelligence purposes; and
- To correctional institutions or law enforcement custodial situations.

To request this list or accounting of disclosures, please contact 855-281-9301 or support@novocure.com. We may request that you submit the request in writing. Your request must state a time period that may not be longer than six years from the date of service. Your request should indicate in what form you want the list (i.e., paper or electronic). The first list you request within a 12-month period will be free. For additional lists, we will charge you for the costs of providing the lists. We will notify you of the cost involved and you may choose to withdraw or modify your request at the time before any costs are incurred.

Right to Request Restrictions

You have the right to request a restriction or limitation on the PHI we use or disclose about you for treatment, payment, or health care operations. You also have the right to request a limit on the PHI we disclose about you to someone who is involved in your care or the payment for your care, like a family member or friend. You may restrict disclosures of PHI to a health plan if you have paid out-of-pocket in full for the health care item or service. We are not required to agree to your request. If we do agree, we will comply with your request unless the information is needed to provide you emergency treatment. Please contact 855-281-9301 or support@novocure.com to request restrictions. We may request a written request. You must tell us i) what information you want to limit, ii) whether you want to limit our use, disclosure or both, and iii) to whom you want the limits to apply, for example, disclosures to your spouse.

Right to Request Confidential Communications

You have the right to request that we communicate with you about medical matters in a certain way or at a certain location. For example, you can ask that we only contact you at work or by mail. Please contact 855-281-9301 or support@novocure.com to request confidential communications. We may request a written request. We will accommodate all reasonable requests. Your request must specify how or where you wish to be contacted.

Right to Revoke Authorization

You have the right, in those instances where written authorization is required, to revoke such authorization to use or disclose PHI except to the extent action has already been taken. Such revocation must be in writing.

Right to a Paper Copy of this Notice

You have the right to a paper copy of this notice. You may ask us to give you a copy of this notice at any time. Even if you have agreed to receive this notice electronically, you are still entitled to a paper copy of this notice. Please contact 855-281-9301 or support@novocure.com to request a paper copy.

How We May Use and Disclose Protected Health Information About You

The following categories describe different ways that we are permitted to use and disclose PHI as a health care provider. Certain of these categories may not apply to our business and we may not actually use or disclose your PHI for such purposes. Not every use or disclosure in a category will be listed. However, all of the ways we are permitted or required to use and disclosure PHI, without your authorization, will fall within one of the categories.

For Treatment

We may use or disclosure PHI about you to assist healthcare professionals and providers provide you with medical treatment or services. For example, we may provide PHI related to your use of our products or services to your physician and the staff at your physician's practice to assist your physician in maintaining appropriate use of the device.

For Payment

We may use and disclose PHI about you so that the products and services we provide you may be billed to and payment may be collected from you, an insurance company or a third party. For example, we may need to receive from or disclose to your health plan, Medicare, or the medical facility you resided in information about the products and services we provided to you so they or another responsible payor can pay us. This may specifically include information required for the Prescription Order Form, Assignment of Benefits,

MRIs, and medical record information. We may also tell your health care provider or plan about a product or service you are going to receive to obtain prior approval or to determine whether your provider or plan will cover that product or service.

For Health Care Operations

We may use and disclose PHI about you for our health care operations and we may use and disclose PHI about you to other health care providers involved in your care for certain health care operations they have to undertake. These uses and disclosures are necessary to run our company and make sure that users of our products receive the most cost effective and therapeutic products possible. Examples of health care operations activities by Novocure include but are not limited to delivery, pick-up and service functions, collection efforts, internal auditing, business planning (including analysis of product length of use, utility, or development/improvement of reimbursement methods or policy), assessing the quality of care and outcomes in your case and similar cases, and quality assurance/improvement activities. We may also combine PHI about many patients to decide what additional products and services we should offer, what products and services are not needed, and to justify how effective our products are in the care of individuals such as you. We may also disclose information to medical facilities and independent researchers for review and learning purposes. We may remove information that identifies you from this set of PHI so others may use it to study health care and health care delivery without learning who the specific patients are.

Notice/Reminders

We may use and disclose PHI to contact you or arrange for your health care provider to contact you regarding product delivery, maintenance, in-service or pick-up.

Individuals Involved in Your Care or Payment for Your Care

We may disclose to a family member, other relative, close personal friend of yours or any other person identified by you PHI directly relevant to such person's involvement with your care or payment for your health care when you are present for, or otherwise available prior to, a disclosure and you are able to make health care decisions, if: (i) we obtain your agreement; (ii) we provide you with the opportunity to object to the disclosure and you failed to do so; or (iii) we infer from the circumstances, based upon professional judgment, that you do not object to the disclosure. We may obtain your oral agreement or disagreement to a disclosure. However, if you are not present, or the opportunity to agree or object to the disclosure cannot practicably be provided because of your incapacity or an emergency circumstance, we may, in the exercise of professional judgment, determine whether the disclosure is in your best interests, and, if so, disclose only PHI that is directly relevant to the person's involvement with your health care.

Research

Under certain circumstances, we may use and disclose PHI about you for research purposes. For example, a research project may involve comparing the health and recovery of all patients who received on product or service for the same condition. We may also disclose PHI about you to people preparing to conduct a research project, for example to help them look for patients with specific medical circumstances. We will in most circumstances ask for your specific authorization if the researcher will have access to your name, address or other identifying information that reveals who you are.

As Required by Law

We will disclose PHI about you when required to do so by federal, state or local law. For example, we may disclose information for judicial and administrative proceedings pursuant to legal authority; to report information related to victims of abuse, neglect or domestic violence; or to assist law enforcement officials in their law enforcement duties.

Government Functions

We may use and disclose PHI about you as required for specialized government functions such as protection of public officials, reporting to various branches of the armed services or national security activities authorized by law.

To Avert a Serious Threat to Health or Safety

We may use and disclose PHI about you when necessary to prevent a serious threat to your health and safety or the health and safety of the public or another person. Any disclosure, however, would only be to someone able to help prevent the threat.

Business Transfers

There may arise in the course of business the acquisition or sale of our business assets (Business Transfers). Such Business Transfers may involve the sale or purchase of PHI. Also, in the event that Novocure Inc. or its parent entity, Novocure™ Limited of Jersey (Channel Islands), or any subsidiary of Novocure Limited are acquired or substantially all of its assets are acquired, PHI likely will be one of the transferred assets.

Workers' Compensation

We may release PHI about you for workers' compensation or similar programs. These programs provide benefits for work-related injuries or illness.

Public Health Activities

We may use or disclose your PHI to a health oversight agency for activities authorized by law. These oversight activities include, for example, audits, investigations, inspections, and licensure. These activities are necessary for the government to monitor the health care system, government programs, and compliance with civil rights laws.

Lawsuits and Disputes

If you are involved in a lawsuit or a dispute, we may disclose PHI about you in response to a court or administrative order. We may also disclose PHI about you in response to a subpoena, discovery request, or other lawful process by someone else involved in the dispute, but only if efforts have been made to tell you about the request and obtain your written authorization or to obtain an order protecting the information requested.

Other Uses of Protected Health Information

Other uses and disclosures of PHI not covered by this notice or otherwise permitted by laws that apply to us will be made only with your written authorization. Your authorization will not be required if Novocure uses or discloses health information for purposes other than as covered by this notice or permitted by law if Novocure removes any information that individually identifies you before disclosing the remaining information. If you provide us authorization to use or disclose PHI about you, you may revoke that permission, in writing, at any time. If you revoke your permission we will no longer use or disclose PHI about you for the reasons covered by your written authorization. You understand that we are unable to take back any disclosures we have already made with your permission, and that we are required to retain our records of the products and services that we provided to you.

Changes to This Notice

We reserve the right to change our information practices and to make the new provisions effective for all PHI we maintain. We also reserve the right to change this notice at any time. We reserve the right to make the revised or changed notice effective for PHI we already have about you as well as any information we receive in the future. You may request current version of our privacy practices by contacting 855-281-9301 or support@novocure.com.

Complaints

If you believe your privacy rights have been violated, you may file a complaint with us or with the Secretary of the Department of Health and Human Services. To file a complaint with us, you must submit it in writing to Novocure. Please contact 855-281-9301 or support@novocure.com to request the current mailing instructions for Novocure.

Patient Bill of Rights

Your Rights

As a patient you have certain rights including but not limited to the following:

- **Information.** Patients have the right to receive accurate, easily understood information to assist them in making informed choices.
- **Choice.** Patients have the right to a choice of health care providers.
- **Access to Emergency Services.** Patients have the right to access emergency health services when and where the need arises.
- **Being a Full Partner in Health Care Decisions.** Patients have the right to participate fully in all decisions related to their health care.
- **Care Without Discrimination.** Patients have the right to considerate, respectful care from all members of the healthcare industry at all times and under all circumstances.
- **Privacy.** Patients have the right to communication with healthcare providers in confidence and to have the confidentiality of their individual identifiable health care information protected.
- **Speedy Complaint Resolution.** Patients have the right to a fair and efficient process for resolving differences.

Your Responsibilities

As a patient you have certain responsibilities including, but not limited to the following:

- **Provide information.** You must give accurate and complete health information concerning your past illnesses, hospital stays, medications, allergies and other pertinent items. You are also responsible for providing documentation required by your insurance company.
- **Ask questions.** You must ask question when you do not understand medical conditions, equipment, instructions, and or medical terminology.
- **Follow instructions.** You must adhere to your developed and updated treatment plans.
- **Accept consequences.** You must accept consequences for not following the treatment plan instructions of your doctor and nurse.
- **Understand your benefits.** You must understand what your insurance company will or will not authorize for durable medical equipment (DME) benefits.
- **Product responsibilities.** Your doctor has prescribed this medical device for the treatment and care of your disease. This is a rental device and cannot be resold. Prompt return of this device is required once therapy is completed.

- **Show respect and consideration.** You must show respect and consideration to those who are assisting you in your treatment plan including Novocure's staff providing technical support for your use of the device.
- **Meet financial commitments.** You are responsible for any applicable co-insurance, co-payments, or private pay amounts not covered by your insurance provider.

Contact Information for Questions or Complaints

Any questions, concerns or complaints may be addressed to: 855-281-9301 (toll-free) or support@novocure.com.

You may contact the Accreditation Commission on Health Care to report any concerns or register a complaint by calling ACHC toll-free at 855-937-2242 or 919-785-1214 and request the Complaints Department.

Authorization to Release Information; Assignment of Benefits; Acknowledgment of Education and Training; Acknowledgment of Receipt of Certain Forms; and Delivery Confirmation

Background

Optune™ (the "System") is comprised of two main components: (1) an Electric Field Generator (the "Device"); and (2) INE Transducer Arrays (the "Arrays") that are disposable supplies to the Device. Novocure™ Inc. is referred to as "we" or "Novocure" in this service agreement ("Service Agreement"). The use of "you" in this Service Agreement refers to the patient named in this Service Agreement.

Authorization to Release Information

You authorize your physician and the practice, facility and hospital of your physician and any other holder of medical information about conditions for which you are being treated to release to Novocure any information necessary for treatment, payment and healthcare operations related to your use of the System. You also authorize Novocure, your physician and the practice, facility and hospital of your physician and any other holder of medical information about conditions for which you are being treated to release such information to your insurance company and any other entity paying for your medical care ("your payer"). These authorizations apply to your current physician and previous physicians, their practices, facilities and hospitals.

Authorization To Discuss Care

You authorize Novocure to discuss your care with the family members and/or caregivers listed below. You may revoke this authorization at any time by calling or emailing Novocure at 855-281-9301 or support@novocure.com.

List all authorized individuals:

Berny Prosser, Daniel Mees

Assignment of Benefits

You give Novocure the right to bill for and receive payments for your medical care and you direct your payer to pay Novocure directly for the System. You agree to forward all payments to Novocure in the event that your payer pays you directly, and you acknowledge that Novocure may stop supplying the

System to you if you fail to do so. You acknowledge receipt of the supply terms and information on financial responsibilities and warranties ("Supply Terms") from Novocure and agree to those terms.

Acknowledgment of Education and Training

You have received education on the use and maintenance of the System. You have been provided a technical support phone number for questions about use of the System. You have been provided with the User Manual for the System. You consent to accept phone calls from Novocure for technical support and health care operations matters, including billing matters.

Acknowledgment of Certain Forms

You acknowledge that you have received, read and accepted all terms and conditions set forth in these documents:

1. **Patient Information Form**, which includes a Statement of Privacy Practices, Patient Bill of Rights, and Contact Information for Novocure for Questions and/or Complaints

We are required by regulation to respond to your complaints within 5 calendar days and respond back to you with the results of our investigation within 14 calendar days.

2. **Supply Terms**, which includes Financial Responsibilities and Warranty information

3. **Advanced Beneficiary Notice**
(for Medicare patients only)

The products and/or services provided to you by Novocure are subject to the supplier standards contained in the Federal regulations shown at 42 Code of Federal Regulations Section 424.57©. These standards concern business professional and operational matters (e.g., honoring warranties and hours of operation). The full text of these standards can be obtained at <http://ecfr.gpoaccess.gov>. Upon request we will furnish you a written copy of the standards."

Please sign here:

Berny Prosser
Signature

6-16-16
Date

Printed on: 10 May 2016, 07:28:05 am; Printed by: BMILLS.

Delivery Confirmation

You acknowledge receipt of the equipment and supplies listed below:

Part Description	Quantity	S/N or Lot Number
Optune™ Device E0766	1	TFH00801
Connection Cable	2	CAD13343 CAD14244
Portable Charger	1	ZCH10698
Power Supply	1	SPS11414
Rack	1	PBL11834
Portable Battery	4	ZBH17598 ZBH19486 ZBH11571 ZBH14609
Black Transducer Array (Lot#) E0766	20	C601203
White Transducer Array (Lot#) E0766	20	C1604101
Device Combo Bag	1	
Power Cord	2	
Manual – Instructions for Use	1	
Operation Manual	1	
Self-Exchange Kit	1	

You agree to the terms of this Service Agreement and of the related forms that you have received.
The authorizations granted in this Service Agreement will expire two (2) years from the date signed below.

Signatures

Patient Name (please print): Anniken Prosser

Patient or authorized signature: Anniken Prosser Date: 6-16-16

If anyone other than patient completes or signs this form, please enter the following information:

Name: _____ Telephone Number: _____

Address: _____

City, State, Zip: _____

Relationship to Patient: _____

Reason for Signing: _____

For Novocure™ Use Only

Delivery Person/Service Print: Nancy Newberg

Signature/Tracking#: Nancy Newberg

Delivery Date: 6/16/16

Novocure Patient ID#: 1012479

Novocure Order #: 18251

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QSF-DME-02114-01 Printed on: 10 May 2016, 07:28:05 am; Printed by: BMILLS.



PATIENT INFORMATION AND CONSENT

Optune™ Treatment Education Visit

IMPORTANT: Please do not sign this consent until you read and understand the consent. Please discuss any questions you may have with the Novocure™ personnel that will conduct your treatment education. You should feel that signing this form is something you are doing voluntarily. If you feel that you are under pressure, please do not sign this form. Please read this consent to understand the purpose and nature of this treatment education visit. If you sign this consent, you confirm that you understand the purpose and nature of this visit and that you give your consent to participate in the treatment education.

You or your physician has requested that Novocure personnel conduct a treatment education visit for Optune. ***If you want to hold this session at your physician's office, please tell Novocure personnel prior to the start of the session and do not sign this consent.***

You (and your caregiver(s)) are being trained regarding the use of Optune. As part of this session, you will be taught about the following:

- Use of Optune, including how to change the battery, how to recharge the battery and connect to an external power supply, how to connect the transducer arrays connectors to the connector box, and what to do when an alarm occurs;
 - How to shave your head to maintain appropriate transducer array contact with your scalp;
 - How to apply the transducer arrays to your scalp; and
 - How to turn Optune "on" and "off"
- By signing this consent, you confirm your understanding that:
- Novocure personnel conducting your treatment education session are not physicians or healthcare providers. Please talk to your

physician regarding your medical care and any questions you may have regarding your medical condition and your treatment options

- Novocure personnel are providing education regarding the use of Optune. You will also receive the Patient Instruction and Operation Manual (PIOM) for Optune, which will be a resource for any questions you may have after this session
- Novocure personnel will teach you and/or your caregiver(s) how to shave your head and apply the transducer arrays. You and/or your caregiver(s) will shave your head and apply the transducer arrays, with assistance from Novocure personnel. Novocure personnel may touch you during the session while teaching you and/or your caregiver(s) to perform these activities
 - You may suffer cuts and possible skin irritation associated with shaving your head
 - You may suffer mild to moderate skin irritation associated with application of the transducer arrays
 - You should contact your physician regarding care for any injury you suffer during this treatment education session

- Novocure personnel will show you and/or your caregiver(s) how to begin therapy by turning Optune "on." It is your decision when to begin Optune therapy. If you initiate therapy today, please initiate therapy in the presence of Novocure personnel, who will confirm Optune is working appropriately.
- If you have a medical issue during the session, you consent to Novocure personnel calling 911 and/or emergency medical services.
- Your physician will confirm that you understand how to use Optune and its use at your next physician visit.

I agree to participate in the treatment education session described and to allow Novocure personnel to conduct the session.

By signing this form, I have not given up any of my legal rights.

Please print your name: Anniken Prosser

6-16-16
(Date)

Anniken Prosser
(Signature of Participant)

novocureTM

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Printed on: 20 May 2016, 07:01:14 am; Printed by: BMILLS. Expiration Date:
FRM-FC-007 REV

novocure

Patient Document Acknowledgement

<i>Document</i>	<i>Initials</i>
1. Service Agreement	<u>ASP</u>
2. Patient Rights and Responsibilities (From service agreement)	<u>ASP</u>
3. Supplier Standards (Medicare only)	<u> </u>
4. Financial review/Assessment (Patient was contacted and these items discussed)	<u>ASP</u>
5. How to file a complaint	<u>ASP</u>

**This form is to be returned to the Commercial Operations Center along with
the signed Service Agreement.**

Technical Review of Optune™

Patient Name: Annika Prosser	Patient #: 1012479
Patient Signature: Annika Prosser	Date: 6-16-16

Optune <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> Overview and Description Powering On/Off

Connection Cable <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> Overview and Description Connecting to Device

Powering the Device <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> Portable Batteries Connecting Power Sources Charging Portable Batteries Battery Rack and Charger Wall Power Supply

Carrier Bag <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> Placement and Carry Options

Transducer Arrays <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> Overview and Description Transducer Array Components Placement Recommendations How to Shift Paired Arrays at Each Array Change Skin Observation and Care Showering Disposal and Reorder

Troubleshooting <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> Alarms Common Causes Correcting Alarms Novocure Support Information Equipment Exchange Process

Placing the Arrays <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> Preparing the Head Review NovoTAL-Map Applying the Transducer Arrays

Patient Literature <input checked="" type="checkbox"/>
<ul style="list-style-type: none"> PIOM Patient Quick Start Guide

Novocure Employee Name: Nancy Newberg	
Novocure Employee Signature: Nancy Newberg	Date: 6/16/16

novocure

TM-MA-002 Rev 06

PAGE 1 of 1

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 Printed on: 20 May 2016, 07:02:02 am; Printed by: BMILLS. Expiration Date:

Case 1:20-cv-00194-WCG Filed 04/28/20 Page 308 of 539 Document 11-6 5170

05-29-'18 16:18 FROM-
 Prosser, Anniken S (MR # 10790724)

T-580 P0002/0015 F-198
 Encounter Date: 03/15/2018

Prosser, Anniken S

MRN: 10790724
 Description: 34 year old female

Progress Notes Encounter Date: 3/15/2018

Connelly, Jennifer M, MD

Neurology

Neuro-Oncology followup Visit

RE: Anniken S Prosser

MR#: 10790724

DOB: 10/10/1983

Date of Clinic Visit: 3/15/2018

Chief Complaint: GBM

History of Present Illness:

Ms. Prosser is a 34 Y/o lady who returns to the Neuro-Oncology clinic for further evaluation and management of a left temporal Grade 4 astrocytoma. She comes to clinic today with her husband and son, Liam. Since her last visit, she has remained on TTFields (compliance 91% for march). She is using clobetasol as needed. They rotate around open lesions. Neurologically, she is doing great with no other symptoms. She has otherwise been healthy.

Neuro-oncology History:

H/o migraines - started in mid-20's; possibly secondary to Crohn's meds; diffuse in nature and daily

Feb. 14, 2016 - intractable migraine

MRI - large left cystic temporal mass

Feb. 25, 2016 - left craniotomy - GBM

May 2016 - completed radiation with Dr. Editha Kruegar with concurrent temodar with Dr. Jasleen Randhawa

June 2016 - continue with adjuvant temodar

June 16, 2016 - started Optune TTFields

April 2017 - completed 12 cycles of temodar; continue TTFields

Past Medical History:

Diagnosis	Date
• Crohn's disease (*)	
• GBM (glioblastoma multiforme)	2/25/16
left temporal	
• WPW (Wolff-Parkinson-White syndrome) 1999	
s/p ablation	

Social History

Social History

• Marital status:	Married
Spouse name:	N/A
• Number of children:	N/A
• Years of education:	N/A

05-29-'18 16:18 FROM-
 PROSSER, ANNICKEN S (VIA # 10790724)

T-580 P0003/0015 F-198
 ENCOUNTER DATE: 03/12/2018

Social History Main Topics

- | | |
|----------------------|--------------|
| • Smoking status: | Never Smoker |
| • Smokeless tobacco: | Never Used |
| • Alcohol use: | Not on file |
| • Drug use: | Unknown |
| • Sexual activity: | Not on file |

Other Topics

- Not on file

Concern

Social History Narrative

- No narrative on file

Family History

Problem	Relation	Age of Onset
• Breast Cancer	Maternal Aunt	
• Ovarian Cancer onset in 20's	Maternal Cousin	
• Cancer onset in 80's - leukemia	Paternal Grandfather	

Current Outpatient Prescriptions

Medication	Sig
• acetaminophen (TYLENOL) 500 MG tablet	Take 500 mg by mouth every 4 hours as needed.
• Calcium Citrate-Vitamin D (CALCIUM + D PO)	Take 1 tablet by mouth daily.
• clobetasol propionate (CLOBEVATE OR TEMOVATE) 0.05 % cream	Apply as needed to scalp rash. Leave on for 20-60 minutes, cleanse lightly with alcohol and apply arrays.
• fish oil	Take 1 tablet by mouth daily.
• Multiple Vitamins-Minerals (WOMENS DAILY MULTIVITAMIN PO)	Take 1 tablet by mouth daily.
• NON FORMULARY MEDICATION	Reasons reishi mushroom for immune support
• TURMERIC CURCUMIN PO	Take 1 tablet by mouth daily. Patient uses brand Curcubrain

Allergies

Allergen

- Ragweed
- Sulfa Drugs

Reactions

EENT - watery eyes
 RESP - shortness of breath

ROS:

Constitutional - denies fevers, weight loss

Eyes - denies diplopia

05-29-18 16:18 FROM-
 Prosser, Anniken S (MR # 10790724)

T-580 P0004/0015 F-198
 Encounter Date: 03/15/2018

Ears, Nose, Mouth, Throat - denies difficulty swallowing
 Cardiovascular - denies chest pain
 Respiratory - denies SOB, cough
 Gastrointestinal - has constipation intermittently while on temodar, this balances the diarrhea caused by Crohns
 Genitourinary - denies dysuria
 Integumentary - has skin breakdown in scalp
 Neurological - as per HPI
 Psych - denies depression, anxiety

Exam:

Vitals:

03/15/18 1429
 BP: 129/87
 Pulse: 85
 Resp: 16
 Temp: 98.2 °F (36.8 °C)
 SpO2: 98%
 Weight: 51.8 kg (114 lb 3.2 oz)

General: no distress.
 Skin: mild contact dermatitis

Neurologic:

Mental Status: Alert and attentive. Oriented to person, place, time and reason for visit. Language fluent with intact comprehension. Immediate recall, working memory, and long-term memory intact. No neglect.

Cranial Nerves:

1 - not assessed
 2 - Fully Intact visual fields bilaterally via confrontation.
 3, 4, 6 - extraocular movements intact and conjugate. Normal smooth pursuit. Normal saccades.
 5 - normal facial sensation to light touch bilaterally.
 7 - symmetric facies with normal smile, palpebral fractures, nasal labial folds and forced eyelid closure.
 8 - grossly intact
 9, 10 - symmetric palate elevation.
 11 - 5/5 head turning, bilaterally.
 12 - tongue midline at rest and upon protrusion.

Motor: 5/5 throughout with normal bulk and tone; no evidence of pronation
 Finger tapping: normal frequency and amplitude bilaterally

Reflexes: 2+ throughout

Sensation: Intact to light touch in all 4 extremities

Motor Integration (Cerebellar):

Finger to Nose: Normal bilaterally without ataxia, dysmetria, or tremor.
 Rapid Alternating Movements: Normal with bilateral hands

Gait:

05-29-'18 16:19 FROM-
 PROSSER, ANNICKEN S (MR # 10790724)

T-580 P0005/0015 F-198
 Encounter Date: 03/15/2018

Normal, not wide-based, no circumduction, no foot drop, no hyperextension of the knee or ankle, no spasticity. No assistive devices.

Karnofsky Performance Score

Able to carry on normal activity and to work; no special care needed - Score = 80% (Normal activity with effort; some signs or symptoms of disease).

ECOG/WHO Score

0 = Fully active, able to carry on all predisease performance without restriction.

Review of Imaging

Mr Brain Wo + W Cont/rCBV Result Date: 3/15/2018

Impression 1. Postoperative changes in the left temporal region are similar to the prior study. Linear enhancement at the posterior medial margin of the left anterior temporal resection cavity similar to the prior study. 2. An area of nonenhancing abnormal long TR signal with gyral expansion in the left lateral and medial temporal lobes and in the left subinsular region, similar to the prior study. No new lesions. 3. No evidence for abnormal vascularity on MR perfusion study.

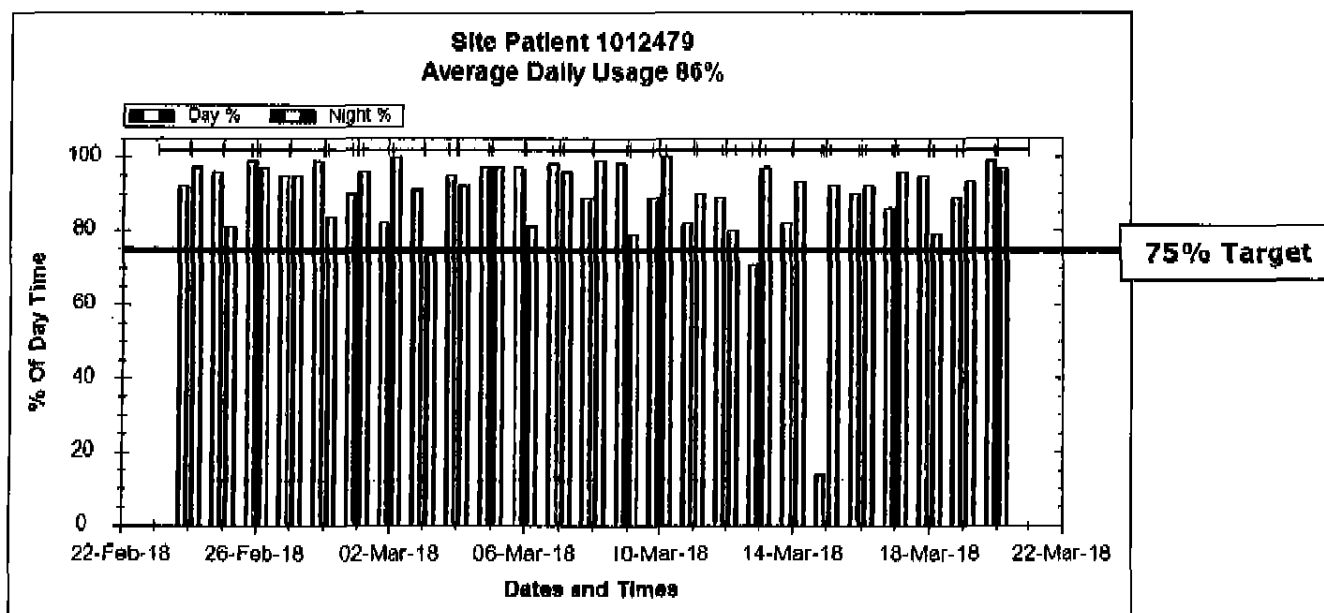
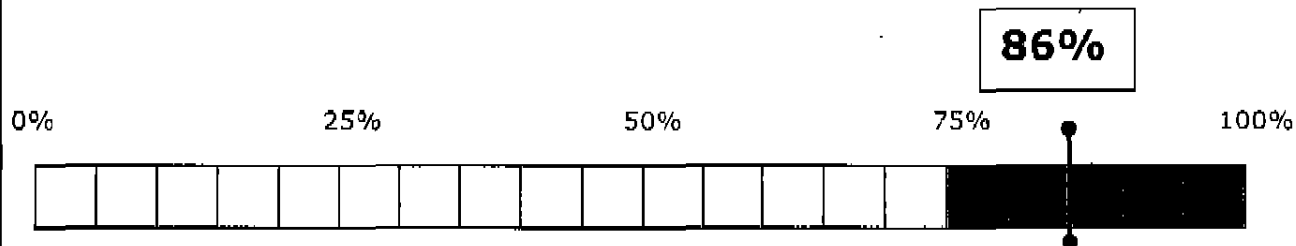
Assessment: Ms. Prosser is a 34 Y/o lady with left temporal GBM on TTFields. She is neurologically intact and radiographically stable. She is tolerating TTFields well and has excellent compliance. She will proceed as outlined below.

Recommendations:

1. GBM - Continue Optune TTFields
 Clobetasol for skin irritation
2. RTC 3 months with MRI

25 minutes spent in evaluation, management and coordination of care of patient of which >50% was counseling.

Office Visit on 3/15/2018 . Note shared with
 patient

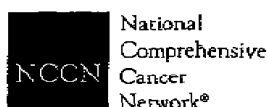
novocure**Patient Compliance Report****Patient Name:** Anniken Prosser**Treating Physician:** Dr. Jennifer Connelly**Treating Institution:** Froedtert Hospital and the Medical College of Wisconsin**Novocure Patient Number:** 1012479**Report Date:** March 21, 2018**Period Covered:** February 24, 2018 - March 20, 2018**Average Daily Usage:****Overall Compliance for the Period:****Report compiled by:** Danita Ziegler

NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®) for

Central Nervous System Cancers

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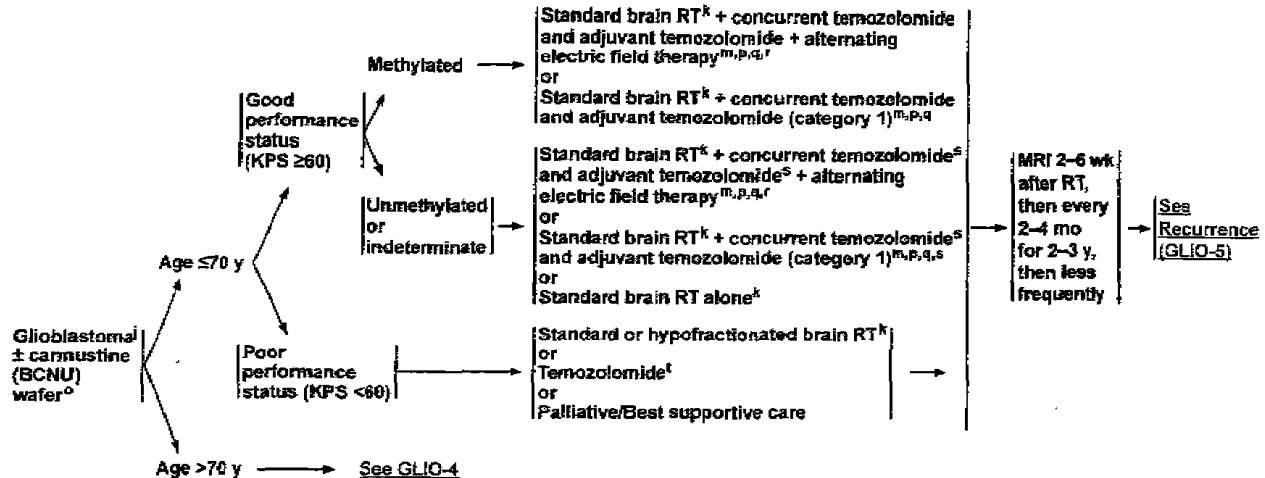


**GLIOBLASTOMA
PATHOLOGY^a**

**MGMT^b PROMOTOR
STATUS**

ADJUVANT TREATMENT

FOLLOW-UP^h



^aThis pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

^bSee Principles of Brain and Spine Tumor Imaging (BRAIN-A).

^cSee Principles of Brain Tumor Pathology (BRAIN-F).

^dThis pathway also includes gliosarcoma.

^eSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

^fSee Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

^gMGMT = O⁶-methylguanine-DNA methyltransferase.

^hTreatment with carmustine wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.

^pCombination of agents may lead to increased toxicity or radiographic changes.

^qBenefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown. The optimal duration of treatment with temozolomide for anaplastic astrocytoma is unknown.

^rAlternating electric field therapy is only an option for patients with supratentorial disease.

^sClinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.

^tTemozolomide monotherapy is only recommended if tumor is MGMT promoter methylated.

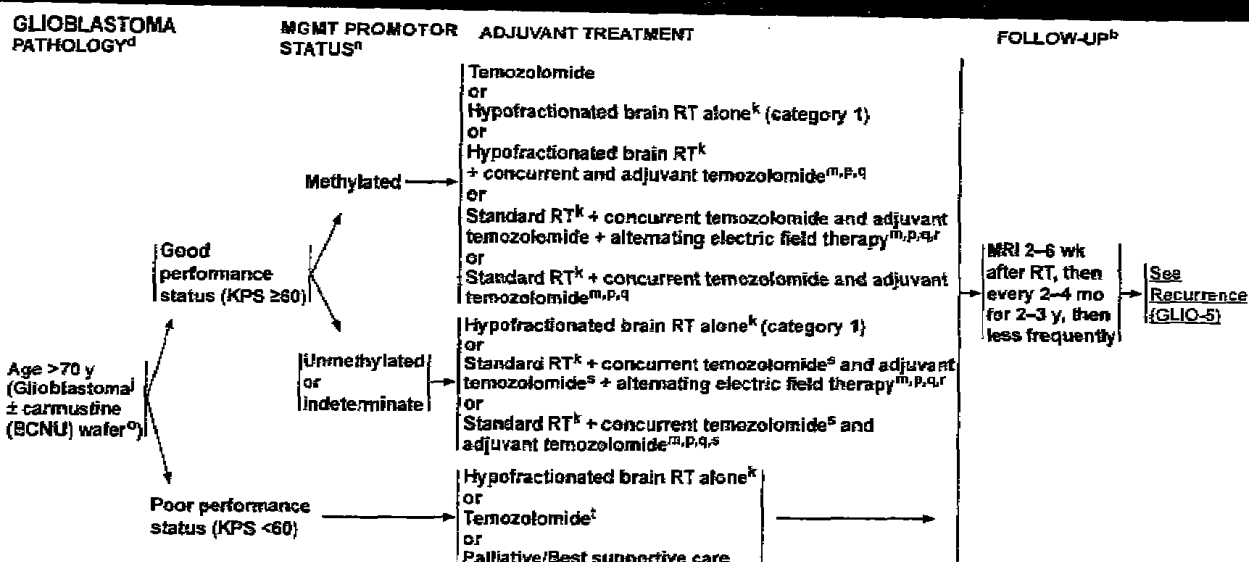
Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GLIO-3

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^aThis pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

^bSee Principles of Brain and Spine Tumor Imaging (BRAIN-A).

^cSee Principles of Brain Tumor Pathology (BRAIN-F).

^dThis pathway also includes gliosarcoma.

^eSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

^fSee Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

^gMGMT = O⁶-methylguanine-DNA methyltransferase.

^hTreatment with carmustine wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.

ⁱCombination of agents may lead to increased toxicity or radiographic changes.

^jBenefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown. The optimal duration of treatment with temozolomide for anaplastic astrocytoma is unknown.

^kAlternating electric field therapy is only an option for patients with supratentorial disease.

^lClinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.

^mTemozolomide monotherapy is only recommended if tumor is MGMT promoter methylated.

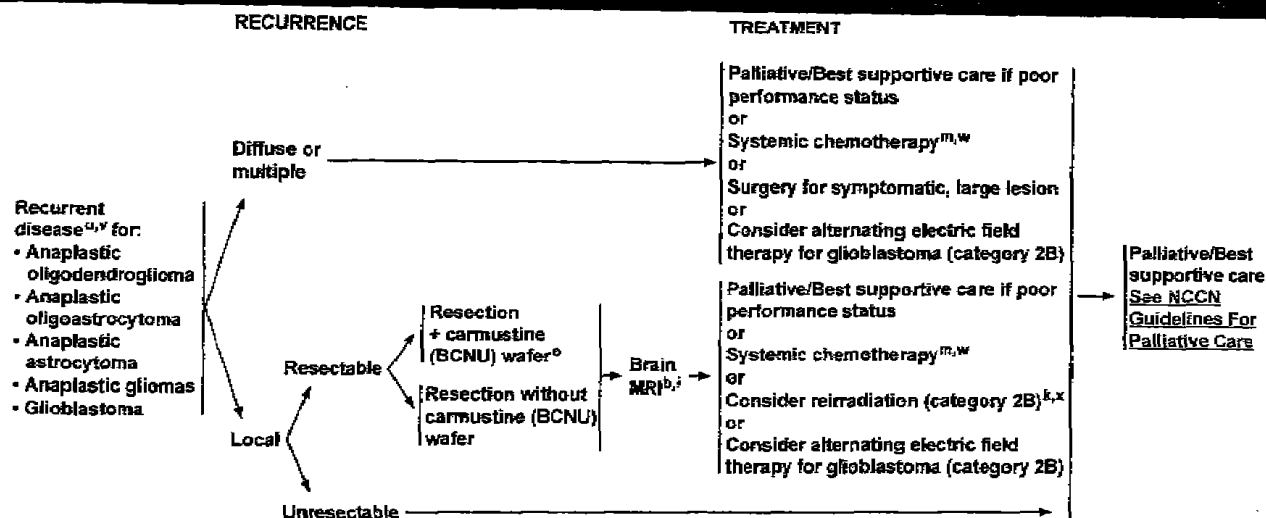
Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GLIO-4

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^aThis pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

^bSee Principles of Brain and Spine Tumor Imaging (BRAIN-A).

ⁱPostoperative brain MRI within 24–72 hours after surgery.

^kSee Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).

^mSee Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).

^oTreatment with carmustine wafer, reirradiation, or multiple prior systemic therapies may impact enrollment in some adjuvant clinical trials.

^uConsider MR spectroscopy, MR perfusion, or brain PET to rule out radiation necrosis.

^wWithin the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging. With pseudoprogression, stabilization or improvement should be expected within 3 mo of the end of radiotherapy.

^xAnaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.

^yEspecially if long interval since prior RT and/or if there was a good response to prior RT.

Note: All recommendations are category 2A unless otherwise indicated.

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GLIO-5

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Journal of the
American Medical Association

Reprint Article

Preliminary Communication

Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew A. Kanner, MD; Santosh Kesari, MD, PhD; David M. Steinberg, PhD; Steven A. Toms, MD, FACS, MPH; Lynne P. Taylor, MD, FAAN; Frank Lieberman, MD; Antonio Silvani, MD; Karen L. Fink, MD, PhD; Gene H. Barnett, MD, MBA; Jay-Jiguang Zhu, MD, PhD; John W. Henson, MD, MBA, FAAN; Herbert H. Engelhard, MD, PhD; Thomas C. Chen, MD, PhD; David D. Tran, MD, PhD; Jan Sroubek, MD; Nam D. Tran, MD, PhD; Andreas F. Hottinger, MD, PhD; Joseph Landolfi, DO; Rajiv Desai, MD; Manuela Caroli, MD; Yvonne Kew, MD, PhD; Jerome Honnorat, MD, PhD; Ahmed Ididath, MD, PhD; Eilon D. Kirson, MD, PhD; Uri Weinberg, MD, PhD; Yoram Palti, MD, PhD; Monika E. Hegl, PhD; Zvi Ram, MD

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PUBLICATION

Research

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Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial

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IMPORTANCE Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Most patients die within 1 to 2 years of diagnosis. Tumor-treating fields (TTFields) are a locoregionally delivered antimitotic treatment that interferes with cell division and organelle assembly.

OBJECTIVE To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229) (median time from diagnosis to randomization, 3.8 months in both groups). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis.

INTERVENTIONS Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m²/d) was given for 5 days of each 28-day cycle.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival in the intent-to-treat population (significance threshold of .01) with overall survival in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). This prespecified interim analysis was to be conducted on the first 315 patients after at least 18 months of follow-up.

RESULTS The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). Median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004).

CONCLUSIONS AND RELEVANCE In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00916409

JAMA. 2015;314(23):2535-2543. doi:10.1001/jama.2015.16669

Editorial page 2511

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Roger Stupp, MD, Department of Oncology and Cancer Center, University Hospital Zurich, CH-8091 Zurich, Switzerland (roger.stupp@usz.ch).

Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Gy) with concomitant daily temozolomide chemotherapy, and then maintenance treatment with temozolomide for 6 to 12 months.¹ However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials.¹⁻⁴ The reported 2- and 5-year survival rates⁵ are 27% and 10%, respectively. During the last decade, all attempts to improve the outcome for patients with glioblastoma have failed when evaluated in large randomized trials.^{2-4,6,7}

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively disrupts the division of cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the shaved scalp.⁸⁻¹⁰ In preclinical models, TTFields have been shown to cause mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis.^{6,10-12} In a randomized phase 3 trial in which TTFields were compared with chemotherapy in 237 patients with recurrent glioblastoma, the use of TTFields did not prolong progression-free survival or overall survival, but the therapy was associated with better quality of life without the typical chemotherapy-associated toxic effects.¹³

Based on preclinical data demonstrating a synergistic antitumor effect with chemotherapy and TTFields, and pilot clinical feasibility data in combination with temozolomide,⁹ we initiated this phase 3 trial. The objective was to evaluate the efficacy and safety of TTFields used in combination with maintenance temozolomide in patients with glioblastoma after initial treatment with temozolomide and radiotherapy.

Methods

Study Population

Patients eligible for this study (1) had histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma¹⁴), (2) were progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and (3) had completed standard concomitant chemoradiotherapy with temozolomide. Other eligibility criteria were (1) age of 18 years or older, (2) Karnofsky Performance Status (KPS) score of 70% or higher (the KPS score describes the general condition of a patient; a KPS score $\geq 70\%$ ensures some independence in activities of daily living), and (3) adequate bone marrow, liver, and renal function.

Prior use of implanted carmustine wafers was allowed. Patients with infratentorial tumor location and severe comorbidities were excluded. All patients provided written informed consent before entering the study; the study was approved by the institutional review boards or ethics committees of all 83 participating centers. The trial protocol appears in Supplement 1.

Study Design and Treatment

This multicenter, open-label, randomized phase 3 trial was designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. After the completion of treatment with temozolomide and radiotherapy, patients were randomized at a ratio of 2 to 1 (Figure 1) to receive standard maintenance temozolomide chemotherapy (150-200 mg/m²/d for 5 days every 28 days for 6-12 cycles according to the protocol¹ from the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group) with or without the addition of TTFields. Treatment with TTFields was to be initiated within 4 to 7 weeks from the last dose of concomitant temozolomide and radiotherapy. Randomization was performed through a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by O⁶-methylguanine-DNA methyltransferase (MGMT) methylation status (methylated, unmethylated, or unknown).

For patients with available paraffin-embedded tumor tissue, evaluation of MGMT gene promoter methylation status was performed as described previously^{7,15,16} by a central laboratory blinded to treatment group (MDxHealth). If MGMT methylation status could not be determined centrally prior to randomization, local MGMT methylation status was used for stratification.

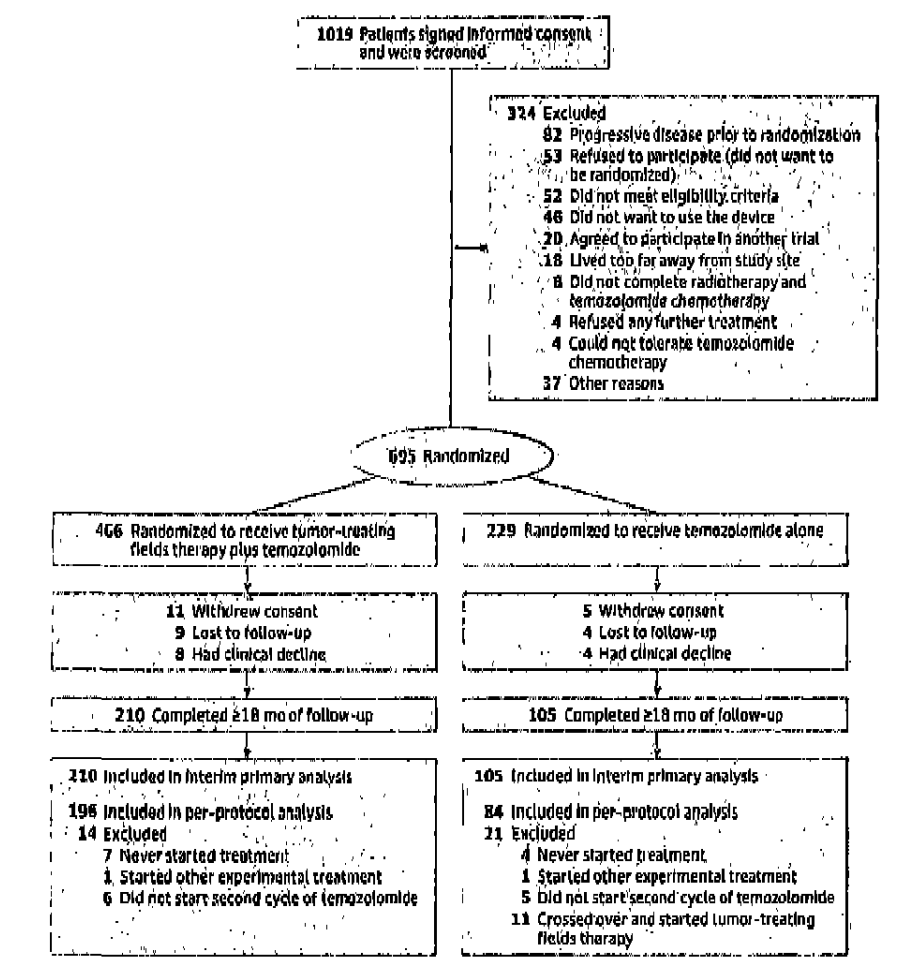
Patients in the TTFields plus temozolomide group received continuous TTFields combined with standard maintenance temozolomide. Patients receiving TTFields had 4 transducer arrays placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Ltd). Transducer array layouts were determined using a mapping software system for TTFields to optimize field intensity within the treated tumor (NovoTAL, Novocure Ltd). After being trained to operate the device, the patient continued treatment at home. The transducer arrays were supplied in sterile packaging and replaced by the patient, a caregiver, or a device technician twice per week. Although uninterrupted treatment was recommended, short treatment breaks for personal needs were allowed.

If a patient experienced tumor progression, second-line chemotherapy was offered per local practice. However, in the TTFields plus temozolomide group, TTFields could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

Patient Surveillance and Follow-up

Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance temozolomide with or without TTFields. A complete physical examination with collection of laboratory parameters was performed within 1 week of treatment initiation. The evaluation also included a quality-of-life questionnaire (QLQ-C30) that has a brain-specific module (BN-20), which was developed by the European Organisation

Figure 1. Recruitment and Inclusion of Patients in the Study



for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups.^{17,18} A Mini-Mental State Examination (a short bedside test used to evaluate cognition and memory) also was administered (a test result of 27-30 points is considered normal function).

Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months. Magnetic resonance imaging was to be performed every second month after the baseline MRI until second radiological progression in all patients. In the event of clinical progression, MRI was to be performed within 1 week after the study investigator became aware of it. All MRIs were reviewed centrally by 2 blinded independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression using the criteria developed by Macdonald et al.¹⁹ In cases in which the central reviewers were not in agreement, a third blinded radiologist adjudicated between them. The third radiologist was involved in 17% of the cases in the TTFields plus temozolomide group and in 18% of the cases in the temozolomide alone group.

The results of the central review were not communicated to the study investigator, and all treatment decisions were based on local imaging interpretation. Eight patients in the

TTFields plus temozolomide group (4%) compared with 6 patients in the temozolomide alone group (3%) were considered stable by blinded central review; however, treatment had been changed by the study investigator due to local interpretation of tumor progression. Patients were removed from the progression-free survival analysis at the date of treatment change when this occurred before evidence of tumor progression or when patients reached the cutoff date without tumor progression.

Adverse events were recorded prospectively according to the National Cancer Institute's Common Terminology Criteria (version 3.0) until 2 months after treatment discontinuation. Adverse events are presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the interim analysis. Treatment adherence with TTFields was recorded electronically by the device as average daily use in hours per day and information was reviewed and transferred at the monthly follow-up visit.

Statistical Considerations

The primary end point was progression-free survival in the intent-to-treat (ITT) population assessed by an independent review panel (80% power; hazard ratio [HR], 0.78; 2-sided α level

of .05). The study was also designed to have 80% power (HR, 0.76; 2-sided α level of .05) to examine overall survival as a secondary end point. To avoid an increase in the risk of a false-positive result, overall survival was to be tested statistically only if the primary end point was met.

This prespecified interim analysis was to be performed after the first 315 randomized patients reached a minimum 18-month follow-up. The final type I error rate of 0.05 was split between the interim and final analyses based on a standard α -spending function.²⁰⁻²² The protocol prespecified that overall survival would be analyzed in an as-treated population, excluding all patients in both treatment groups who (1) never started maintenance temozolomide, (2) had major protocol violations, (3) crossed over to the other treatment group, or (4) received TTFields outside the protocol setting.

The primary end point would be achieved in the interim analysis if progression-free survival in the ITT population was significantly longer in the intervention group compared with the control group using a stratified log-rank test with an α level of .01. The secondary end point would be achieved in the interim analysis if overall survival in the as-treated population (per-protocol population) was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an α level of .006. The confidence intervals that go with the HRs are presented as 1 minus the prespecified α level for each analysis. For example, the α level in the per-protocol interim analysis for overall survival was .006. Therefore, the corresponding confidence interval used for presenting the HRs was 1.000 - 0.006 (99.4% confidence interval). An upper confidence limit of less than 1 indicates the prespecified statistical threshold was met. An independent data and safety monitoring committee was chartered to stop the trial if the interim analysis of progression-free survival (ITT population) and overall survival (per-protocol population) surpassed these predetermined thresholds, as well as for futility or safety concerns.

In addition to these prespecified analyses, an analysis of overall survival in the ITT population was performed. Furthermore, a robustness analysis including all 695 patients enrolled in the trial served to validate the findings of the interim analysis (database lock: December 29, 2014; eAppendix 1 in Supplement 2).

Multiple imputation analyses also were performed for the trial's primary end point of progression-free survival in the ITT population to test the sensitivity of the results to possible bias using informative and interval censoring. These analyses included (1) treating all patients with informative censoring as treatment failures in the TTFields plus temozolomide group, (2) censoring all patients with informative censoring in the temozolomide alone group (worst case scenario), and (3) treating all events in the TTFields plus temozolomide group and in the temozolomide alone group as occurring differentially at different periods during the inter-MRI interval before the date of tumor progression.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.1.1.²³ The final analysis will be performed when all 695 patients enrolled in the study have at least 18 months of follow-up and will include prespeci-

fied subgroup analyses and additional secondary end points, including quality of life.

Results

Study Participants

Between July 2009 and November 2014, there were 695 patients with newly diagnosed glioblastoma randomized to receive either TTFields plus temozolomide ($n = 466$) or temozolomide alone ($n = 229$). Data for the interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 to temozolomide alone (Figure 1; database lock: September 5, 2014). The independent data and safety monitoring committee met in October 2014 to review the interim analysis; the trial met the predefined boundaries for success (improvement of both progression-free and overall survival) and the committee recommended study termination, thus allowing patients in the control group to crossover and receive TTFields.

After approval of study termination by the US Food and Drug Administration, the trial was closed to recruitment on November 29, 2014, after 695 patients of the planned 700 patients had already been randomized. All patients in the control group with ongoing maintenance therapy were offered to receive TTFields. At the time of this report, 35 patients in the control group crossed over to receive TTFields. Follow-up for all patients continues according to the protocol.

Patient baseline characteristics were well balanced between the 2 groups (Table 1). The median age was 57 years and 66% were male. The median KPS score was 90%. Sixty-four percent of patients had a gross total resection and 11% had only a diagnostic biopsy. Tumor tissue for central MGMT testing was available for 72% of the patients; the MGMT methylation frequency was 39% (75/191 valid tests; 39% for the TTFields plus temozolomide group and 41% for the temozolomide alone group). Tumor location in the brain was also comparable.

Carmustine wafers (Gliadel) were used at initial surgery in 2.4% of patients in the TTFields plus temozolomide group vs 2.9% of patients in the temozolomide alone group. Ninety-five percent of the patients were white and 61% were treated in the United States. The rest of the patients were treated at centers in Canada, Europe, Israel, and South Korea. The median time from diagnosis to randomization was 3.8 months (range, 2.0-5.7 months) for patients in the TTFields plus temozolomide group and 3.8 months (range, 1.4-5.7 months) for those in the temozolomide alone group. The median time from the end of treatment with temozolomide and radiotherapy to randomization was 36 days in the TTFields plus temozolomide group and 38 days in the temozolomide alone group; 53% of patients were randomized after having started the first cycle of maintenance temozolomide. The median time from randomization to initiation of TTFields was 5 days.

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the TTFields

Table 1. Patient Baseline Characteristics and Treatment Details

	All Patients (N = 315)	TTFIELDS Plus Temozolomide (n = 210)	Temozolomide Alone (n = 105)
Age, y			
Mean (SD)	55.8 (11.1)	55.3 (11.3)	56.8 (10.5)
Median (range)	57 (20-83)	57 (20-83)	58 (21-80)
Karnofsky Performance Status score, median (range), %^a	90 (60-100)	90 (60-100)	90 (70-100)
Sex, No. (%)			
Male	207 (66)	140 (67)	67 (64)
Female	108 (34)	70 (33)	38 (36)
Use at baseline, No. (%)			
Antiepileptic medication	126 (40)	88 (42)	38 (36)
Corticosteroid therapy	77 (24)	51 (24)	26 (25)
Mini-Mental State Examination score, No. (%)^b			
≤26	45 (15)	31 (15)	14 (13)
27-30	247 (78)	174 (83)	73 (70)
Unknown	23 (7)	5 (2)	18 (17)
Extent of resection, No. (%)			
Biopsy	34 (11)	23 (11)	11 (10)
Partial resection	79 (25)	52 (25)	27 (26)
Gross total resection	202 (64)	135 (64)	67 (64)
Tissue available and tested, No. (%)	227 (72)	152 (72)	75 (71)
MGMT methylation	75 (33)	49 (32)	26 (35)
No methylation	116 (51)	79 (52)	38 (51)
Invalid test result	36 (16)	24 (16)	11 (15)
Region, No. (%)			
United States	191 (61)	127 (60)	64 (61)
Rest of world	124 (39)	83 (40)	41 (39)
Completed radiation therapy, No. (%)			
<57 Gy	18 (6)	13 (6)	5 (5)
60 Gy (standard; ±5%)	291 (92)	191 (91)	100 (95)
>63 Gy	6 (2)	6 (3)	0 (0)
Concomitant temozolomide use, No. (%)			
Yes	308 (98)	207 (99)	101 (96)
Unknown	7 (2)	3 (1)	4 (4)
Time from event to randomization, median (range), d			
Last day of radiotherapy	37 (13-68)	36 (13-53)	36 (13-68)
Initial diagnosis	114 (43-171)	115 (59-171)	113 (43-170)
No. of maintenance temozolomide cycles until first tumor progression, median (range)	6 (1-26)	6 (1-26)	4 (1-24)
Duration of treatment with TTFIELDS, median (range), mo	9 (1-58)	9 (1-58)	
Adherence to TTFIELDS therapy ≥75% during first 3 mo of treatment		157 (75)	

Abbreviations: MGMT, O⁶-methylguanine-DNA methyltransferase; TTFIELDS, tumor-treating fields.

^a A higher score indicates better functional status.

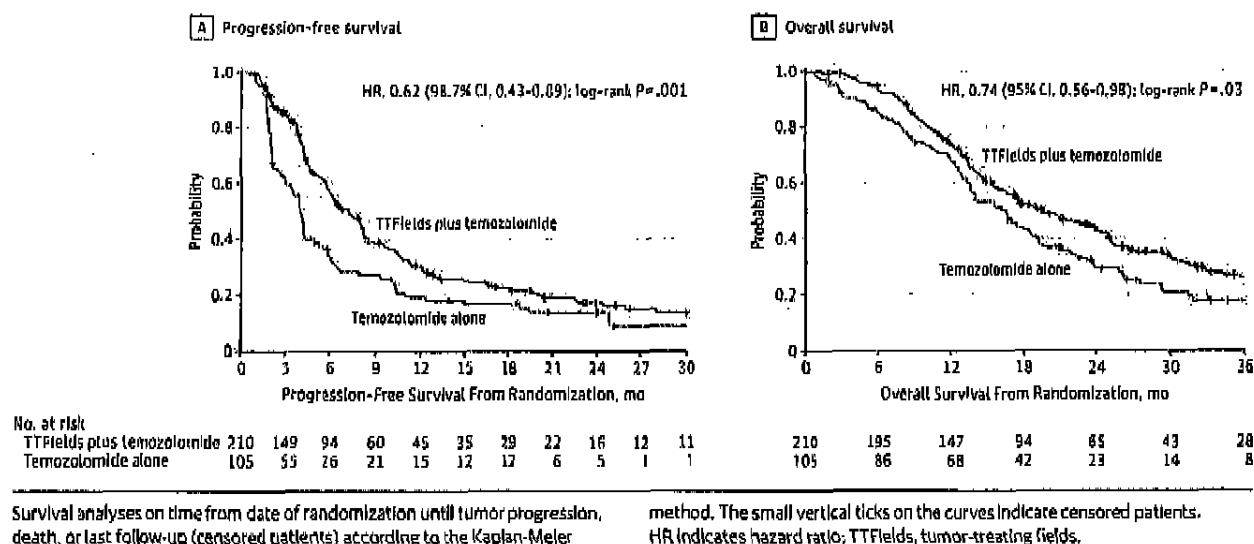
^b A higher score indicates better cognitive capability.

plus temozolomide group and 4.0 cycles (range, 1-24 cycles) for patients in the temozolomide alone group; the median duration of treatment with TTFIELDS was 9 months (range, 1-58 months). Two-thirds (n = 141) of patients in the TTFIELDS plus temozolomide group continued treatment with TTFIELDS after first tumor progression. Three-quarters (n = 157) of patients receiving treatment with TTFIELDS were adherent to therapy (ie, wearing the device >18 hours per day on average during the first 3 treatment months).

Efficacy End Points

As prespecified, the primary end point for the efficacy results was based on progression-free survival in the ITT population of the interim analysis data set. After a median follow-up of 38 months (range, 18-60 months), the median progression-free survival from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the TTFIELDS plus temozolomide group compared with 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (HR, 0.62 [98.7% CI, 0.43-0.89];

Figure 2. Survival Curves for Patients Included in the Interim Analysis in the Intent-to-Treat Population



stratified log-rank $P = .001$; Figure 2A). Thus, adding TTFIELDS to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

As per the statistical analysis plan, overall survival was to be tested in a prespecified per-protocol population only after the primary end point was found to surpass the threshold for significance in the interim analysis. Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFIELDS plus temozolomide group ($n = 196$) compared with 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group ($n = 84$) (HR, 0.64 [99.4% CI, 0.42-0.98]; stratified log-rank $P = .004$). The details on the per-protocol population and analyses are summarized in eAppendix 2 in Supplement 2.

In additional analyses in the ITT population, the median overall survival was 19.6 months (95% CI, 16.6-24.4 months) in the TTFIELDS plus temozolomide group compared with 16.6 months (95% CI, 13.6-19.2 months) in the temozolomide alone group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank $P = .03$; Figure 2B). The percentage of patients alive at 2 years following enrollment was 43% in the TTFIELDS plus temozolomide group and 29% in the temozolomide alone group ($P = .006$).

To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Patient characteristics of all patients randomized did not differ significantly from the interim data set, and the results for the main end points were similar in these analyses compared with the interim analysis (eAppendix 1 in Supplement 2).

Second-line treatments, such as nitrosoureas, temozolomide rechallenge, and bevacizumab, were received by 67% of the patients in the TTFIELDS plus temozolomide group compared with 57% in the temozolomide alone group; about 40% of second-line therapies included bevacizumab and about 40% included nitrosoureas. The type of chemotherapy used at recurrence was balanced between treatment groups.

Secondary imputation analyses of progression-free survival with relation to the effects of interval and informational censoring did not change the conclusions of the primary progression-free survival analysis (eAppendix 3 in Supplement 2).

Safety and Tolerability

The addition of TTFIELDS to temozolomide therapy in patients with newly diagnosed glioblastoma was not associated with any significant increase in systemic toxic effects compared with temozolomide therapy alone (Table 2). The overall incidence, distribution, and severity of adverse events were similar in patients treated with TTFIELDS plus temozolomide and in those treated with temozolomide alone. The only notable exception was a higher incidence rate of localized skin toxicity (medical device site reaction beneath the transducer arrays) in patients treated with TTFIELDS plus temozolomide. Mild to moderate skin irritation was observed in 43% of patients treated with TTFIELDS plus temozolomide and severe skin reaction (grade 3) in 2%. Mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFIELDS plus temozolomide and occurred mainly at the time of therapy initiation. The incidence of seizures was almost identical in the 2 groups (15 [7%] in the TTFIELDS plus temozolomide group vs 8 [8%] in temozolomide alone group). A total of 12 patients died of causes considered unrelated to treatment while receiving adjuvant therapy (8 [3.9%] in the temozolomide plus TTFIELDS group and 4 [4.0%] in the temozolomide alone group; Table 2).

Discussion

Glioblastoma is a highly aggressive brain tumor affecting men and women, frequently at the peak of life. Prognosis remains poor with no major treatment advance in more than a decade. In the interim analysis of this randomized clinical trial,

the addition of TTFields to standard maintenance temozolomide significantly improved progression-free and overall survival. The prespecified analyses revealed that patients randomized to receive TTFields plus temozolomide compared with patients randomized to receive temozolomide alone had a median progression-free survival of 7.1 months vs 4.0 months (ITT analyses). Patients who received TTFields plus temozolomide had a median overall survival of 20.5 months compared with 15.6 months in those who received temozolomide alone (as per the prespecified per-protocol analysis; the ITT analysis did not differ substantially).

Based on the results of this planned interim analysis, the trial's independent data and safety monitoring committee recommended termination of the trial. Because almost all patients had been enrolled (695/700) in the study by the time the recommendation was implemented, the full trial population will be followed up for both progression-free and overall survival. Subsequent analyses of all secondary end points and subgroups will be performed when the follow-up data are available.

The trial population and the results in the control group in this study were comparable with other glioblastoma clinical trials. Nevertheless, patients in this trial were randomized only after the end of radiochemotherapy, and for most, the first cycle of maintenance temozolomide had been started at the time of randomization; thus, patients with early tumor progression during radiochemotherapy were excluded. Most glioblastoma trials have reported survival from the date of initial diagnosis or study enrollment before starting radiochemotherapy, thus 3 to 4 months before randomization of the current study.

When the interval from diagnosis to randomization is added to the outcome results in this study, the progression-free survival of 7.8 months in the control group is comparable with most other reported studies, and supports the generalizability of these results. The Radiation Therapy Oncology Group (RTOG) 0525 protocol randomized patients only after the end of treatment with temozolomide and radiotherapy, similar to our study.³ The control groups with standard dose temozolomide only in these 2 trials were comparable: progression-free survival from randomization of 4.0 months in the present study and 5.5 months in the RTOG 0525 trial and overall survival of 16.6 months in both trials. Thus, the benefit observed with TTFields cannot be simply attributed to patient selection. In the present trial, the gain of 3 months in both median progression-free survival (from 4.0 months to 7.2 months; HR, 0.62) and median overall survival (from 16.6 months to 19.6 months; HR, 0.74), translating into a survival gain at 2 years of 14% (from 29% to 43%) in the ITT population is in the range of benefit that is considered clinically meaningful for therapeutic agents in oncology.

The prespecified analysis for overall survival in the interim analysis was to be based on the per-protocol population ($n = 280$); ie, removal in both study groups of the patients who did not start their second course of maintenance temozolomide or had major protocol violations. This analysis met the prespecified threshold for efficacy in the interim analysis for the per-protocol population. In a more conserva-

Table 2. Grade 3 to 4 Treatment-Emergent Adverse Events

	No. (%) of Patients With Adverse Events ^a	
	TTFields Plus Temozolomide ($n = 203$) ^b	Temozolomide Alone ($n = 101$) ^c
Hematological disorders^d	25 (12)	9 (9)
Anemia	1 (<1)	2 (2)
Leukopenia or lymphopenia	11 (5)	5 (5)
Neutropenia	6 (3)	1 (1)
Thrombocytopenia	19 (9)	3 (3)
Cardiac disorders	2 (1)	3 (3)
Eye disorders	2 (1)	1 (1)
Gastrointestinal disorders^d	11 (5)	2 (2)
Abdominal pain	2 (1)	0
Constipation	2 (1)	0
Diarrhea	1 (<1)	2 (2)
Vomiting	3 (1)	1 (1)
General disorders	17 (8)	5 (5)
Fatigue	8 (4)	4 (4)
Infections	10 (5)	5 (5)
Injury and procedural complications^d	14 (7)	5 (5)
Fall	6 (3)	2 (2)
Medical device site reaction	4 (2)	0
Metabolism and nutrition disorders	7 (3)	3 (3)
Musculoskeletal disorders	8 (4)	3 (3)
Nervous system disorders^d	45 (22)	25 (25)
Seizure ^e	15 (7)	8 (8)
Headache	4 (2)	2 (2)
Psychiatric disorders^d	9 (4)	3 (3)
Anxiety	2 (1)	0
Bradypnea	0	1 (1)
Confusional state	2 (1)	1 (1)
Mental status changes	4 (2)	1 (1)
Psychotic disorder	2 (1)	0
Respiratory disorders	4 (2)	1 (1)
Skin disorders	0	1 (1)
Vascular disorders^d	8 (4)	8 (8)
Deep vein thrombosis	1 (<1)	3 (3)
Pulmonary embolism	4 (2)	6 (6)

Abbreviation: TTFields, tumor-treating fields.

^a Safety is reported on patients who have received any treatment. Randomized patients who never received any maintenance therapy were excluded from this safety analysis.

^b Eight patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and infection; and 4 patients with central nervous system disorders likely due to tumor progression).

^c Four patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and unknown).

^d Patients may have had more than 1 adverse event so subcategories do not total and not all events are subcategorized.

tive analysis using the ITT population, an overall survival benefit was also manifest. Furthermore, an analysis of robustness performed on all randomized patients enrolled at the time

of study termination (eAppendix 1 in Supplement 2) supports the conclusions of the interim analysis.

This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

This analysis reports a planned interim analysis on data from the first 315 patients with at least 18 months of follow-up; however, for detailed and meaningful subgroup analyses, the mature data of the full data set will be needed. Treatment failure patterns, effects of second-line therapies, and additional molecular analyses on baseline tumor biopsies will allow for better understanding of the clinical effects of this novel treatment modality. With the last patient randomized on November 29, 2014, however, these data are not expected before the end of 2015.

This was an open-labeled study. A sham or placebo treatment for the control group was considered neither practical (patients would be able to sense heat when they were receiving TTFields) nor appropriate (due to the burden for patients and caregivers and the need to shave the scalp and have transducer arrays placed). In this respect, the trial resembles studies evaluating radiation therapy. This raises the question of a placebo effect leading to the improved outcome. Although some effect of placebo may be expected on subjective end points, such as cognitive function and quality of life, objective end points, such as overall and progression-free survival (assessed by a blinded review panel), are independent of pla-

cebo effects in cancer therapy.²⁴ The panel did not have information on treatment received and no stigmata of TTFields array pads were evident on MRI.

Recent randomized studies of patients with glioblastoma, which did not use placebo controls, failed to show any increase in progression-free or overall survival^{3,7} despite intensive treatment regimens requiring twice weekly hospital visits.⁷ The magnitude of effect size seen in the present trial (HR of 0.62 for progression-free survival and 0.74 for overall survival) is beyond what could be attributed to a placebo effect. In addition, the support provided to patients in the TTFields plus temozolomide group by device support specialists during the trial was largely technical in nature and did not include medical supportive care. Medical follow-up with monthly visits was the same for both treatment groups.

Because TTFields were applied only to the head, an increase in systemic adverse events was neither seen nor expected. No increase in seizure rate or neurological adverse events was observed. Almost half of the patients treated with TTFields did experience some grade 1 to 2 (mild to moderate) localized skin reaction related to the application of the transducer arrays used to deliver the TTFields. This adverse effect could be managed using published skin care guidelines for patients receiving TTFields.²⁵ Only 2% of patients receiving TTFields had grade 3 to 4 (severe) skin reactions beneath the transducer arrays.

Conclusions

In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

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Author Contributions: Drs Stupp and Ram had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Study supervision: Stupp, Kliron, Weinberg, Hegi, Ram.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for

Disclosure of Potential Conflicts of Interest: Dr Stupp reported receiving travel assistance from Novocure for data review and presentation of the results at medical meetings; and receiving personal fees for serving on advisory boards for Roche/Genentech, Merck KGaA, Merck & Co, and Novartis. Dr Taillibert reported receiving personal fees from Mundipharma EDO and Roche. Dr Kanner reported receiving institutional grant funding and personal fees for speaking and device training from Novocure. Dr Kesari reported receiving institutional grant funding and personal fees for consulting and attending advisory meetings from Novocure. Dr Steinberg reported receiving consulting fees from Novocure for performing the statistical analysis. Dr Toms reported receiving personal fees from Novocure for serving on an advisory board. Dr Lieberman reported receiving institutional grant funding from Novocure. Dr Fink reported receiving personal fees from Novocure for serving on an advisory board; and receiving personal fees from Genentech for serving in the speakers program. Dr Zhu reported receiving institutional grant funding and personal fees from Novocure. Dr Engelhard reported receiving institutional grant funding and personal fees from Novocure. Dr Chen reported receiving grant funding, personal fees, nonfinancial support, and being a stock holder and chief

oncology officer in Pharma-kinesis; and receiving grant funding, personal fees, nonfinancial support, and being a stock holder in and CEO of NeOn Technologies. Dr David Tran reported receiving grant funding from Celldex, NWBioTech, Novocure, and Merck; and receiving personal fees from Novocure and PRIME Oncology. Dr Hottelinger reported receiving travel reimbursement and speakers fees from Novocure and Merck Sharp & Dohme; and receiving personal fees for serving on an advisory board for Roche. Dr Landolfi reported receiving personal fees from Novocure for serving on an advisory board. Dr Honorat reported receiving trial support from Novocure and serving on an advisory board for Novocure. Dr Idhah reported receiving grants from Fondation ARC pour la recherche sur le Cancer; receiving research support from IntselChimos and Beta-Innov; receiving personal fees from Novartis for attending a conference; receiving travel reimbursement from Hoffmann-La Roche; and serving as an editorial advisory board member for *Lettre du Cancérologue*. Drs Kirson, Weinberg, and Palti reported being employees of Novocure. Dr Palti also reported holding 35 issued US patents and minority stock ownership in Novocure. Dr Hegl reported receiving institutional grant funding from Novocure, Merck Sharp & Dohme, Roche, and Merck-Serono; and nonfinancial support from MDxHealth for sample testing. Dr Ram reported receiving institutional grant funding from Novocure; and serving as a paid consultant for and holding stock options in Novocure. Drs Taylor, Silvani, Barnett, Henson, Sroubek, Nam Tran, Desai, Carroll, and Kew reported having no disclosures.

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Role of the Funder/Sponsor: Novocure Ltd had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The study was designed by the first and last authors (R.S. and Z.R.), together with representatives from Novocure (mainly E.D.K.). The study oversight was supported and monitored by a clinical research organization (CRO), who also holds the database. Data were collected by the investigators and monitored by the CRO. Device use data were downloaded monthly and transferred to the study investigators or their research staff by device support specialists from Novocure Ltd. The data were analyzed separately by the statistician of the independent data monitoring committee and the study statistician (D.M.S.). Data interpretation was the responsibility of the first and last authors (R.S. and Z.R.), together with the study sponsor representative and project lead (E.D.K.). These 3 physicians also jointly developed the first draft. A subsequent mature draft and a prefinal version were circulated among all authors who gave additional input, contributed to, and approved the manuscript. The first and last authors (R.S. and Z.R.) and E.D.K. had full access to all data, and also reviewed all patient profiles for consistency (R.S. and E.D.K.). The decision to publish the data followed the independent data and safety monitoring committee recommendation for data release, and was supported by all coauthors.

The roles of employees of Novocure are described in the respective author contributions. Other employees' involvement was limited to technical support of the device.

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Indications For Use and Safety Information In the United States:

Please visit www.optune.com/IFU for Optune Instructions For Use (IFU) for complete information regarding the device's indications, contraindications, warnings and precautions.

Optune is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery, and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune is indicated following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Summary of Important Safety Information**Contraindications**

Do not use Optune in patients with an active implanted medical device, a skull defect (such as, missing bone with no replacement), or bullet fragments. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune in patients that are known to be sensitive to conductive hydrogels. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions

Optune can only be prescribed by a healthcare provider that has completed the required certification training provided by Novocure (the device manufacturer).

Do not prescribe Optune for patients that are pregnant, you think might be pregnant or are trying to get pregnant, as the safety and effectiveness of Optune in these populations have not been established.

The most common (≥10%) adverse events involving Optune in combination with temozolomide were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression.

Use of Optune in patients with an inactive implanted medical device in the brain has not been studied for safety and effectiveness, and use of Optune in these patients could lead to tissue damage or lower the chance of Optune being effective.

If the patient has an underlying serious skin condition on the scalp, evaluate whether this may prevent or temporarily interfere with Optune treatment.

Indications for use and safety information in Europe:**Newly diagnosed GBM**

Optune is intended for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant temozolomide, concomitant to maintenance temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant temozolomide. Treatment may be given together with maintenance temozolomide (according to the prescribing information in the Temodar package insert) and after maintenance temozolomide is stopped.

Recurrent GBM

Optune is intended for the treatment of patients with recurrent GBM who have progressed after surgery, radiotherapy and temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy or chemotherapy.

Contraindications

Do not use Optune if you are pregnant, think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune was not tested in pregnant women. Do not use Optune if you have clinically significant hepatic, renal or hematologic disease. Do not use Optune if you have significant additional neurological disease (primary seizure disorder, dementia, progressive degenerative neurological disorder, meningitis or encephalitis, hydrocephalus associated with increased intracranial pressure). Do not use Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Treatment Kit may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings and Precautions

Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). All servicing procedures must be performed by qualified and trained personnel.

Do not use Optune Treatment Kit if you are 17 years old or younger. The system has not been tested in persons 17 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

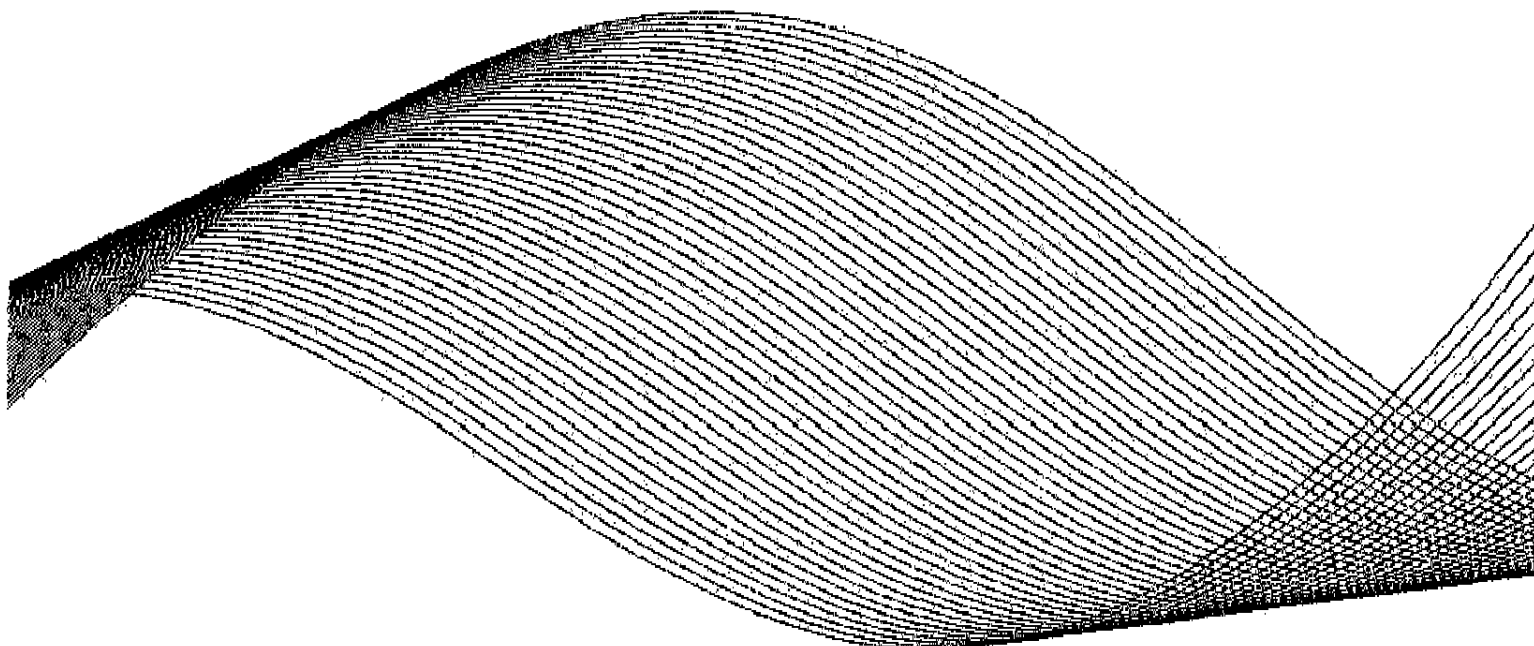
Do not wet the device or the transducer arrays. Do not use any parts that do not come with the Optune treatment kit, or that were not sent to you by the device manufacturer or given to you by your doctor.

Optune commonly causes skin irritation beneath the transducer arrays and in rare cases lead to headaches, falls, fatigue, muscle twitches or skin ulcers.

For complete information regarding Optune's indication, contraindication, warnings and precautions please see the [Instructions for Use \(IFU\)](http://www.optune.com/deutsch/materialien/schulungen.aspx). (<http://www.optune.com/deutsch/materialien/schulungen.aspx>)



INSTRUCTIONS FOR USE



novocure™

This manual is intended for physicians prescribing the use of Optune.
Additional information is found in the following materials:
• Patent Information and Operation Manual

Caution: Federal law restricts this device to sale by or on the order of a physician.

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Indications for Use

Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune™ with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

For the treatment of recurrent GBM, Optune™ is indicated following histologically-or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Contraindications, Warnings and Precautions

Contraindications

Do not use Optune if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement) or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts. Use of Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective.

Do not use Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

Warning – Use Optune only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). Ask to see a certificate signed by Novocure that says they completed a training course. Your training will include a detailed review of this manual and practice in the use of the system. In addition, you will be trained in what to do if there are problems with treatment. Use of Optune without receiving this training can result in breaks in treatment and may rarely cause increased scalp rash, open sores on your head, allergic reactions or even an electric shock.

Warning – Optune is not intended to be used as a substitute for chemotherapy but rather as an adjunct to treatment with TMZ for newly diagnosed GBM.

Warning - Do not use Optune if you are 21 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.

Warning - Do not use Optune if you are pregnant, you think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant or if it will be effective.

Warning - In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), use high potency topical steroids (hydrocortisone cream) when replacing transducer arrays. This will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin break down, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals. Taking a break from treatment may lower your chance to respond to treatment.

Warning - All servicing procedures must be performed by qualified and trained personnel. If you attempt to open and service the system alone you may cause damage to the system. You could also get an electric shock by touching the inner parts of the device.

Precautions

Caution - Keep Optune out of the reach of children. If children touch the device, they could damage the device. This could cause a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution - Do not use any parts that do not come with the Optune Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

Caution - If your doctor used plates or screws to close your skull bone during your surgery, be careful when placing the transducer arrays. Make sure the round disks that make up the transducer arrays are not on top of the areas where you can feel the screws or plates under your skin. In other words, make sure the screws or plates under your skin are in between the round disks that make up the transducer arrays. If you do not do this, you may have increased skin damage which may lead to a break in treatment. Breaks in treatment may lower the chance of the device being effective.

Caution - Tell your doctor before using the device if you have an inactive implanted medical device in the brain (for example, stents, plastic drug delivery reservoirs, aneurysm clips or coils, device leads). Use of Optune in subjects with inactive implanted medical devices in their brain was not been tested and could lead to tissue damage or lower the chance of the device being effective.

Caution - Do not use Optune if any parts look damaged (torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Use of damaged components can damage the device, and cause a break in treatment. Breaks from treatment may lower your chance to respond to treatment.

Caution - Do not wet the device or transducer arrays. Getting the device wet may damage it, preventing you from receiving treatment for the right amount of time. Getting the transducer arrays very wet is likely to cause the transducer arrays to come loose from your head. If this happens, the device will turn off and you will need to change the transducer arrays.

Caution - Before connecting or disconnecting the transducer arrays, make sure that the Optune power switch is in the OFF position. Disconnecting transducer arrays with the device power switch in the ON position may cause a device alarm to go off, and could damage the device.

Caution - If you have an underlying serious skin condition on the scalp, discuss with your doctor whether this may prevent or temporarily interfere with Optune treatment.

Notices

Notice! The Optune device and transducer arrays will activate metal detectors.

Notice! Do not use Optune if your tumor is located in the lower parts of the brain close to the spinal cord. Ask your doctor if your tumor is located in this part of your brain. Optune has not been tested in patients with tumors in these locations. It is unknown whether these tumors will respond to treatment.

Notice! You should use Optune for at least 18 hours a day to get the best response to treatment. Using Optune for less than 18 hours a day lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune before you finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances that you will respond to treatment.

Notice! Do not stop using Optune even if you have used it less than the recommended 18 hours per day. You should stop using the device only if your doctor tells you to. Stopping treatment could lower the chances that you will respond to treatment.

Notice! If you plan to be away from home for more than 2 hours, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Make sure you have at least 12 extra transducer arrays at all times. This will last you until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left. If you do not order transducer arrays in time you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1.5 hours from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! You should carry the Troubleshooting Guide (Section 26) at all times. This guide is necessary to ensure Optune works properly. If you do not work the system correctly you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Do not block the device vents located on the sides of the Optune device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device.

Notice! Do not block the battery charger vents located on the front of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging.

Notice! Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off.

Notice! The transducer arrays are for single use and should not be taken off your head and put back on again. If you put a used transducer array back on your head again, it may not stick well to your skin and the device could turn off.

Description

Optune, for the treatment of newly diagnosed and/or recurrent GBM, is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields ("TTFields") within the human body. TTFields are applied to the patient by electrically-insulated surface transducer arrays. TTFields disrupt the rapid cell division exhibited by cancer cells¹.

Optune is comprised of two main components: (1) an Electric Field Generator (the Optune device); and (2) INE Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included in the Optune Treatment Kit: power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

Treatment parameters are preset by Novocure such that there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week and the scalp re-shaved in order to maintain optimal contact. Patients carry the device in an over-the-shoulder bag or backpack and receive continuous treatment without changing their daily routine.

Principles of Operation

Optune produces alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp.

TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTField technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM).

In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. It is noted that, because TTFields are only applied to the brain, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature. Thus, TTField application has the advantage of being highly selective and is not expected to be associated with significant toxicity.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature.

Preclinical Data

TTFields have been shown both in vitro and in vivo to effectively inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to effectively inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed), due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase².

Specifically, TTFields have been shown to inhibit glioblastoma cells in vitro and in vivo at a frequency of 200 kHz and an intensity of 0.7 V/cm. Based on realistic finite element mesh simulations and direct measurements of TTFields intensity in experimental animals, and in the human brain, Novocure has concluded that effective TTField intensities can be generated in the brains of large animals and humans. Extensive safety studies in healthy animals (mice, rats and rabbits) have shown that TTFields are not associated with significant systemic toxicities. Neither acute, nor chronic systemic toxicities were seen when TTFields were applied to the torso or head, at different frequencies (100-200 kHz), different intensities and for different periods of time³.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for Optune has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

2 Kirson, E. D., Z. Guryich, et al. (2004). "Disruption of cancer cell replication by alternating electric fields." *Cancer Res* 64(9): 3249-55. 5199
3 Kirson, E. D., V. Dabaly, et al. (2007).

Clinical Data

NEWLY DIAGNOSED GLIOBLASTOMA (see page 17 for recurrent GBM)

Pilot Clinical Study in Newly Diagnosed GBM

Optune together with temozolomide (TMZ) has been tested in ten newly diagnosed GBM subjects in a single center, pilot study in Europe. Median progression free survival (PFS) of the patients in this study exceeded historical controls (14.4 months versus 7.1 months, respectively). At the end of the study (4 years from initiation) 5 of the 10 patients died; of the remaining 5 patients 2 were lost to follow up and 3 were reported alive and progression free. Median OS from diagnosis was greater than 40 months (compared to 14.7 months in historical controls). The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device transducer arrays.

Pivotal Clinical Study in Newly Diagnosed GBM

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of newly diagnosed GBM subjects treated with Optune and Temozolomide (TMZ) to those treated with TMZ alone.

The following were the objectives of the study:

To prospectively compare the progression free survival and overall survival of newly diagnosed GBM subjects treated with Optune and TMZ to those treated TMZ alone,

To collect evidence of the safety of TTFields applied to subjects with newly diagnosed GBM using Optune,

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows:

Inclusion Criteria

- a. Pathological evidence of GBM using WHO classification criteria,
- b. ≥ 18 years of age.
- c. Received maximal debulking surgery and radiotherapy concomitant with Temozolomide (45-70Gy):
 - 1) Patients may enroll in the study if received Gliadel wafers before entering the trial
 - 2) Any additional treatments received prior to enrollment will be considered an exclusion.
 - 3) Minimal dose for concomitant radiotherapy is 45 Gy
- d. Karnofsky scale ≥ 70
- e. Life expectancy at least 3 months
- f. Participants of childbearing age must use effective contraception.
- g. All patients must sign written informed consent.
- h. Treatment start date at least 4 weeks out from surgery.
- i. Treatment start date at least 4 weeks out but not more than 7 weeks from the later of last dose of concomitant Temozolomide or radiotherapy.

Exclusion Criteria

- a. Progressive disease (according to MacDonald Criteria). If pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression.
- b. Actively participating in another clinical treatment trial
- c. Pregnant
- d. Significant co-morbidities at baseline which would prevent maintenance Temozolomide treatment:
 - 1) Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
 - 2) Neutropenia (absolute neutrophil count $< 1.5 \times 10^3/\mu\text{L}$)
 - 3) CTC grade 4 non-hematological Toxicity (except for alopecia, nausea, vomiting)
 - 4) Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
 - 5) Total bilirubin $>$ upper limit of normal
 - 6) Significant renal impairment (serum creatinine $> 1.7 \text{ mg/dL}$)
- e. Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias.
- f. Infra-tentorial tumor
- g. Evidence of increased intracranial pressure (midline shift $> 5\text{mm}$, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
- h. History of hypersensitivity reaction to Temozolomide or a history of hypersensitivity to DTIC.

Study Procedures:

Treatment Arm

Optune was given together with maintenance TMZ. At treatment initiation patients were seen at an outpatient clinic. During this visit baseline examinations were performed and Optune treatment initiated. The patients were instructed on the operation of Optune and battery replacement. Once the patients were trained in operating the device they were released to continue treatment at home. The patients received multiple 1 month courses of continuous Optune treatment. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Patients were treated with maintenance TMZ according to the standard dosing regimen. Following radiological progression or unacceptable toxicity, TMZ could be replaced with best standard of care second line therapy.

Follow-up

During treatment all patients were seen once every month at an outpatient clinic where they underwent medical follow-up and routine laboratory exams. An MRI was performed every second month following the baseline MRI until second progression or 24 months (whichever came first, when treatment on both arms of the study was terminated). In the case of clinical progression an unscheduled MRI was obtained within 1 week of the investigator becoming aware of the clinical progression. No additional MRIs were required after second progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months after treatment termination in order to capture treatment related toxicities. After these visits, mortality was assessed based on monthly telephone interviews with the patients or the patients' caregivers.

Analyses: Two analyses were performed in the study: An interim analysis on the first 315 patients with a minimum of 18 months follow up and a final analysis on the full study cohort of 695 patients.

Protocol Deviations: Major protocol deviations were defined as deviations that have the potential to influence the primary and secondary efficacy endpoints of the study. There were a total of 13 major protocol deviations in the interim analysis and a total of 24 major protocol violations at the final analysis.

In the interim analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 11 patients in the TMZ alone arm received Optune treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

In the final analysis dataset, 2 patients received experimental chemotherapies as part of other clinical trials together with their standard of care temozolomide (1 in each treatment arm). In addition, 22 patients in the TMZ alone arm received Optune treatment through prescription at other institutions. This deviation was termed "crossover" although no official crossover was allowed in the protocol, and Optune therapy was given without sponsor or investigator consent.

Analysis Populations: Progression free survival was analyzed in the intent to treat (ITT) population which included all randomized subjects (210 Optune / TMZ and 105 TMZ alone at the interim analysis, 466 Optune / TMZ and 229 TMZ alone at the final analysis). Overall survival was analyzed in the per protocol (PP) population which included all patients receiving at least the first course of TMZ and had no major protocol deviations (196 Optune / TMZ and 84 TMZ alone at the interim analysis; 429 Optune / TMZ and 180 TMZ alone at the final analysis). Major protocol deviations included patients who received other experimental therapies on protocol or crossed over from the TMZ alone arm to Optune / TMZ.

Subject Characteristics: 315 subjects (210 Optune/TMZ; 105 TMZ) with newly diagnosed GBM were enrolled in the Interim analysis of the study. Baseline characteristics in the ITT population were as follows:

Baseline Characteristics	Treatment Group	
	Optune/TMZ (N=210)	TMZ Alone (N=105)
Gender		
Male	140 (66.67)	67 (63.81)
Female	70 (33.33)	38 (36.19)
Central MGMT Assessment		
Invalid	24 (11.43)	11 (10.48)
Unknown	58 (27.62)	30 (28.57)
Methylated	49 (23.33)	26 (24.76)
Unmethylated	79 (37.62)	38 (36.19)
Extent of Resection		
Biopsy	23 (10.95)	11 (10.48)
Gross Total Resection	135 (64.29)	67 (63.81)
Partial Resection	52 (24.76)	27 (25.71)
Area		
ROW	83 (39.52)	41 (39.05)
USA	127 (60.48)	64 (60.95)
Tumor Position		
Missing	0 (0)	3 (2.86)
Corpus Callosum	12 (5.71)	3 (2.86)
Frontal Lobe	64 (30.48)	32 (30.48)
Occipital Lobe	7 (3.33)	4 (3.81)
Parietal Lobe	35 (16.67)	27 (25.71)
Temporal Lobe	92 (43.81)	36 (34.29)
Tumor Location		
Missing	0 (0)	1 (0.95)
Both	2 (0.95)	1 (0.95)
Corpus Callosum	8 (3.81)	3 (2.86)
Left	93 (44.29)	41 (39.05)
Right	107 (50.95)	59 (56.19)
Karnofsky Performance Score	Median	90
	Min, Max	60, 100
Age in Years	Median	57
	Min, Max	20, 83
No. of Cycles of TMZ Received	Median	6
	Min, Max	1, 26
No. of Cycles of Optune Received	Median	9
	Min, Max	1, 58
Time from GBM Diagnosis to Randomization (Days)	Median	115
	Min, Max	59, 171

As seen above, all baseline characteristics are well balanced between arms in the ITT population at the interim analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 35 patients (11.11%) had tissue that was not evaluable, and 88 patients (27.94%) did not have tissue available for analysis.

695 subjects (466 Optune / TMZ; 229 TMZ alone) with newly diagnosed GBM were enrolled in the study and had CRF information available at the time of the final analysis. Baseline characteristics in the ITT population were as follows:

Baseline Characteristics		Treatment Groups	
		Optune/TMZ (N=466)	TMZ Alone (N=229)
Gender			
Male		316 (67.81)	157 (68.56)
Female		150 (32.19)	72 (31.44)
Central MGMT Assessment			
Invalid		46 (9.87)	18 (7.86)
Unknown		106 (22.75)	57 (24.89)
Methylated		127 (27.25)	67 (29.26)
Unmethylated		187 (40.13)	87 (37.99)
Extent of Resection			
Biopsy		61 (13.09)	30 (13.1)
Gross Total Resection		253 (54.29)	124 (54.15)
Partial Resection		152 (32.62)	75 (32.75)
Area			
ROW		245 (52.58)	111 (48.47)
USA		221 (47.42)	118 (51.53)
Tumor Position			
Missing		31 (6.65)	15 (6.55)
Corpus Callosum		21 (4.51)	9 (3.93)
Frontal Lobe		142 (30.47)	67 (29.26)
Occipital Lobe		14 (3)	4 (1.75)
Pariental Lobe		77 (16.52)	50 (21.83)
Temporal Lobe		181 (38.84)	84 (36.68)
Tumor Location			
Missing		30 (6.44)	12 (5.24)
Both		12 (2.58)	3 (1.31)
Corpus Callosum		12 (2.58)	7 (3.06)
Left		193 (41.42)	93 (40.61)
Right		219 (47)	114 (49.78)
Karnofsky Performance Score	Median	90	90
	Min, Max	60, 100	70, 100
Age in Years	Median	56	57
	Min, Max	19, 83	19, 80
No. of Cycles of TMZ Received	Median	5	4
	Min, Max	1, 26	1, 24
No. of Cycles of Optune Received	Median	6	0
	Min, Max	1, 58	0, 0
Time from GBM Diagnosis to Randomization (Days)	Median	113	111
	Min, Max	59, 498	43, 500

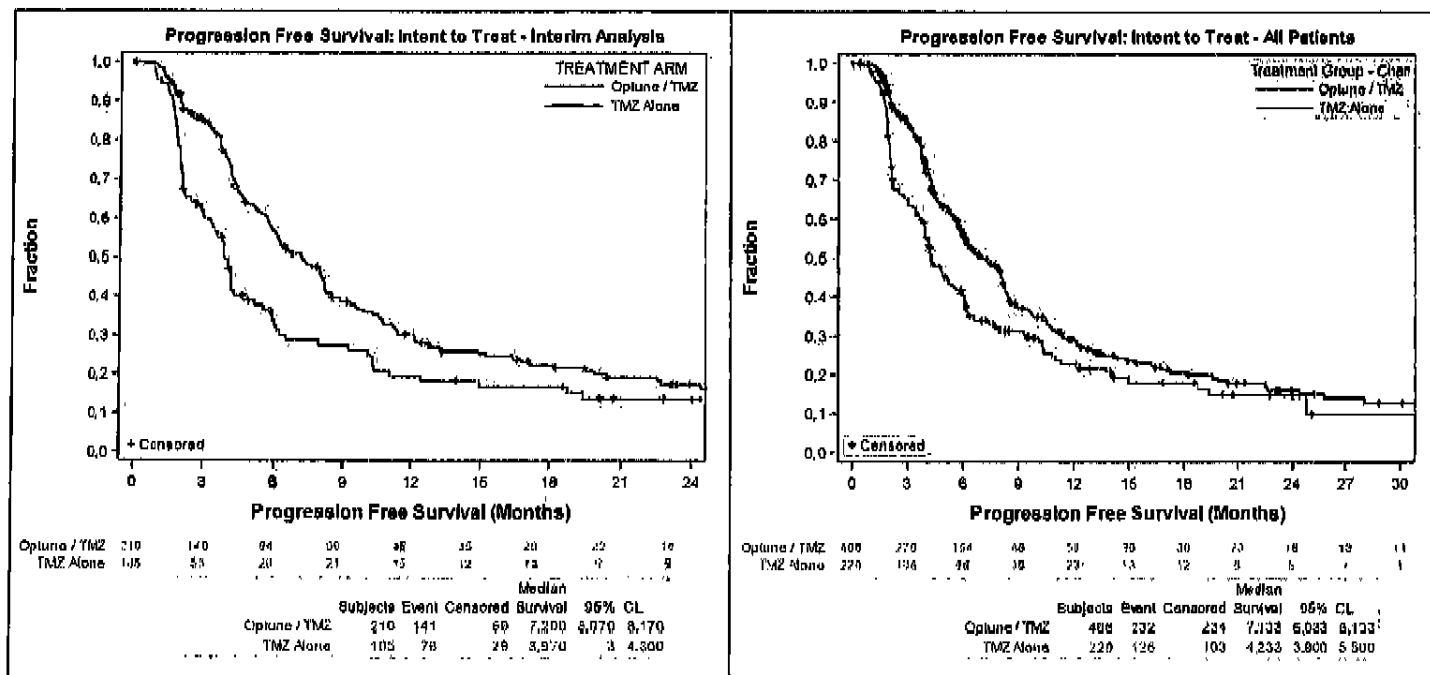
As seen above, all baseline characteristics are well balanced between arms in the ITT population at the final analysis. The baseline characteristics of the PP population also remained well balanced between treatment arms. As noted in the table above, 64 patients (9.21%) had tissue that was not evaluable, and 163 patients (23.45%) did not have tissue available for analysis.

Effectiveness Results:

Primary Effectiveness Endpoint: Progression Free Survival at the Interim Analysis

The threshold for statistical significance based on the Lan-DeMets O'Brien-Fleming method at the interim analysis was pre-defined as $p=0.01394$, and the test was to be performed in the ITT population according to the protocol. In the ITT population, which included all randomized subjects (Optune/TMZ=210, TMZ alone=105), PFS at the interim analysis met this threshold. The difference of more than 3 months in median PFS is highly clinically significant. The Hazard Ratio for PFS was 0.621, which translates into a 37.9% decrease in the risk of progression when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 695 patients (Optune/TMZ=466, TMZ alone=229), PFS was also highly significant with a hazard ratio of 0.694.

Primary Efficacy Endpoint - Progression Free Survival (ITT)

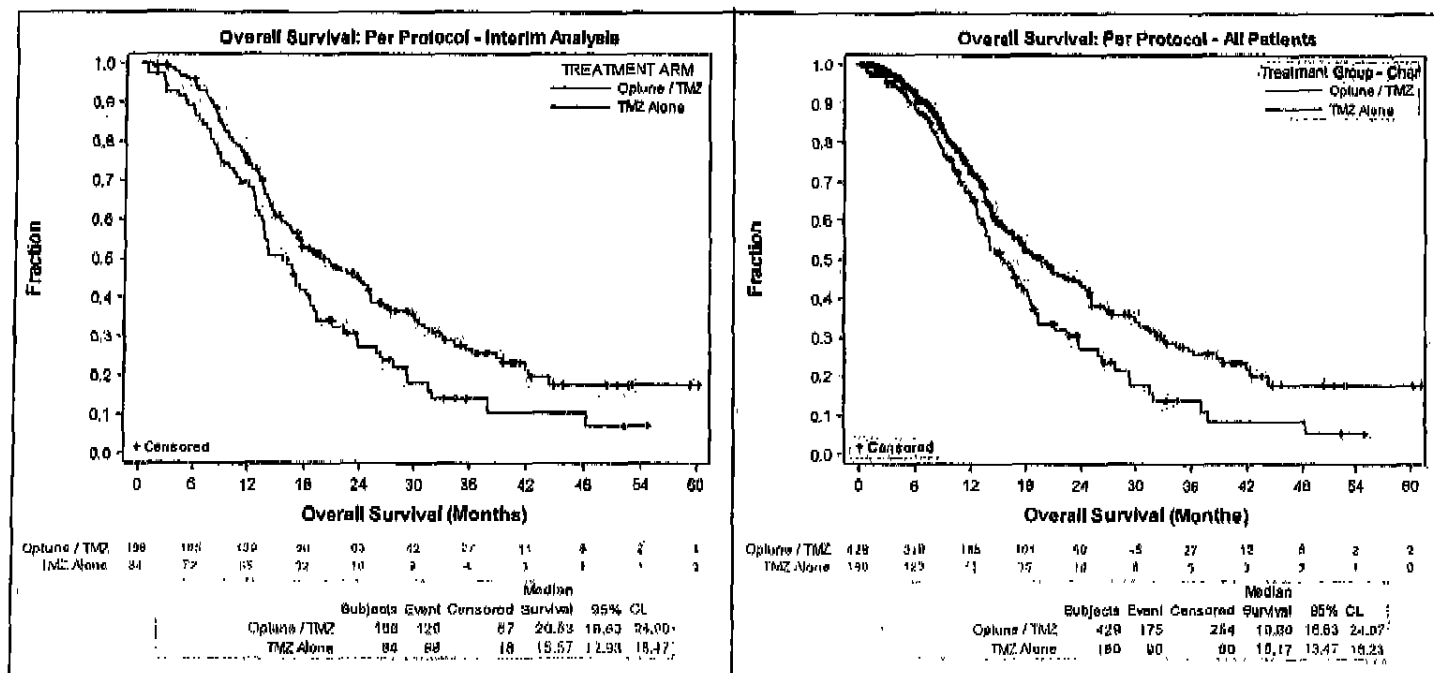


	Interim Analysis		Final Analysis	
	Optune/TMZ	TMZ Alone	Optune/TMZ	TMZ Alone
Median (95% CI)	7.2 (5.9, 8.2)	4.0 (3.0, 4.3)	7.1 (6.0, 8.1)	4.2 (3.9, 5.5)
Log-rank test	p=0.0013		p=0.0010	
Hazard Ratio (95% CI)	0.621 (0.468, 0.823)		0.694 (0.558, 0.823)	

Although not a pre-specified endpoint, PFS was also analyzed in the PP population at the interim and final analyses. Median PFS in the PP population was identical to the ITT population at the interim analysis and slightly longer than the ITT population at the final analysis. Notably, median PFS remained significantly higher in the Optune/TMZ group than in the TMZ alone group in the PP population at both the interim and final analyses.

Powered Secondary Effectiveness Endpoint: Overall Survival at the Interim Analysis

Overall survival (OS) was a powered secondary analysis in the trial. The threshold for superior OS at the interim analysis was predefined in the protocol at 0.00598 according to the Lan-DeMets-O'Brien-Fleming alpha spending function, and was to be tested in the PP population. In the PP population, which analyzed patients according to the treatment they actually received (as treated, Optune/TMZ=196, TMZ=84), OS was also significantly longer in the Optune/TMZ arm compared to the TMZ alone arm. An increase of almost 5 months as seen here is highly significant clinically. The hazard ratio for OS was 0.666. This translates into a 33.4% decrease in the risk of death when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 609 patients (Optune/TMZ=429, TMZ alone=180), OS was also highly significant with a hazard ratio of 0.683.

Overall Survival (PP)

	Interim Analysis		Final Analysis	
	Optune/TMZ	TMZ Alone	Optune/TMZ	TMZ Alone
Median (95% CI)	20.5 (16.6, 24.9)	15.6 (12.9, 18.5)	19.6 (16.6, 24.1)	15.2 (13.5, 18.2)
Log-rank test	p=0.0042		p=0.0030	
Hazard Ratio (95% CI)	0.666 (0.495, 0.898)		0.683 (0.529, 0.882)	

Although not a pre-specified secondary endpoint, OS was also analyzed in the ITT population. At the interim analysis, OS in the ITT population was also significantly longer in the Optune/TMZ arm compared to TMZ alone by almost 20%. The median OS was 19.6 months (95% CI 16.6-24.1) in the Optune/TMZ group and 16.6 months in the TMZ alone group (95% CI 13.5-19.1). An increase of 3 months as seen here is highly significant both statistically (log-rank $p=0.0338$) and clinically. The hazard ratio for OS was 0.744 using a Cox regression analysis. This translates into a 25.6% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

Furthermore, at the final analysis, OS in the ITT population was also significantly longer in the Optune/TMZ arm compared to TMZ alone by 17%. The median OS was 19.4 months (95% CI 16.5-23.8) in the Optune/TMZ group and 16.6 months in the TMZ alone group (95% CI 13.7-18.5). An increase of almost 3 months as seen here is highly significant statistically and clinically (log-rank $p=0.0229$). The hazard ratio for OS was 0.754 using a Cox regression analysis. This translates into a 24.6% decrease in the risk of death when using Optune/TMZ compared to TMZ alone.

Secondary Endpoints: Secondary endpoints also showed an advantage for Optune/TMZ compared to TMZ alone. The results below are from the interim analysis which included 315 patients (210 Optune/TMZ and 105 TMZ alone):

Endpoint	Optune/TMZ	TMZ Alone	P-Value
Progression Free Survival at 6 months (ITT)	56.7%	33.7%	0.0004
1-year survival (PP)	75%	69%	0.151
2-year survival (PP)	48%	32%	0.0058
Complete response rate (ITT)	9%	3.5%	NA

In addition, although not a pre-specified endpoint, 1- and 2-year survival were also analyzed in the ITT population at the interim analysis. In the ITT population, 1-year survival was 75% in the Optune/TMZ group and 70% in the TMZ alone group (p-value=0.162) at the interim analysis. 2-year survival in the ITT population at the interim analysis was 48% in the Optune/TMZ group and 34% in the TMZ alone group (p-value=0.0122). Furthermore, the 1-year survival rates at the final analysis are shown in the table below:

Endpoint	Optune/TMZ	TMZ Alone	P-Value
1-year survival (PP)	69%	63%	0.131
1-year survival (ITT)	69%	66%	0.265

Quality of Life: Quality of Life assessments were based on the interim analysis cohort of 315 subjects. Quality of life, cognitive function and functional status were all maintained throughout treatment with the device, leading to the clear conclusion that use of Optune does not harm patients' quality of life, cognitive function or ability to perform activities of daily living.

Safety Results: Safety was assessed on all patients at the final analysis who received any treatment at the time of the analysis (Optune/TMZ=137, TMZ alone=207). A slightly higher incidence of grade 1-2 adverse events was seen in some of the systems in the Optune/TMZ arm of the study. This is most likely a reflection of the longer duration of TMZ treatment in these patients (median of 6 cycles versus 4 cycles in the control arm) due to the increase in PFS seen in the treatment group. Grade 3-5 adverse events were well balanced between arms. None of the grade 3-5 adverse events in these body systems were considered related to Optune by any of the investigators except for 1% grade 3 skin irritation.

All Adverse Events by Body System and Severity (Safety Population)

System/Organ Class	Optune/TMZ (N=137)			TMZ/TMZ (N=207)		
	Low	Medium	Severe	Low	Medium	Severe
Number of Patients with ≥1 AE	214 (49%)		169 (39%)	15 (3%)	91 (44%)	82 (40%)
						7 (3%)
Blood and Lymphatic System Disorders	86 (20%)		47 (11%)	0	49 (24%)	21 (10%)
Cardiac Disorders	12 (5%)		4 (1%)	3 (1%)	6 (3%)	4 (2%)
Ear and Labyrinth Disorders	25 (6%)		0	0	8 (4%)	0
Endocrine Disorders	11 (3%)		0	0	4 (2%)	0
Eye Disorders	36 (8%)		3 (1%)	0	15 (7%)	2 (1%)
Gastrointestinal Disorders	202 (46%)		18 (4%)	0	76 (37%)	4 (2%)
General Disorders and Administration Site Conditions	175 (40%)		27 (6%)	1 (<1%)	76 (37%)	10 (5%)
Hepatobiliary Disorders	1 (<1%)		1 (<1%)	0	5 (2%)	0
Liver Disorder	1 (<1%)		0	0	3 (1%)	0
Immune System Disorders	10 (2%)		0	0	7 (3%)	0
Infections and Infestations	117 (27%)		19 (4%)	3 (1%)	50 (24%)	6 (3%)
Injury, Poisoning and Procedural Complications	216 (49%)		20 (5%)	0	13 (6%)	4 (2%)
Abnormal Laboratory Tests	58 (13%)		19 (4%)	0	26 (13%)	7 (3%)
Metabolism and Nutrition Disorders	89 (20%)		12 (3%)	0	44 (21%)	6 (3%)
Musculoskeletal and Connective Tissue Disorders	98 (22%)		16 (4%)	0	44 (21%)	8 (4%)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	5 (1%)		1 (<1%)	2 (<1%)	2 (1%)	1 (<1%)
Nervous System Disorder	190 (43%)		83 (19%)	3 (1%)	75 (36%)	42 (20%)
Psychiatric Disorders	108 (25%)		16 (4%)	0	38 (18%)	6 (3%)
Renal and Urinary Disorders	42 (10%)		0	0	8 (4%)	2 (1%)
Reproductive System and Breast Disorders	8 (2%)		0	0	3 (1%)	0
Skin and Subcutaneous Tissue Disorders	104 (24%)		0	0	32 (15%)	1 (<1%)
Surgical and Medical Procedures	2 (<1%)		0	0	2 (1%)	0
Vascular Disorders	48 (11%)		16 (4%)	1 (<1%)	19 (9%)	10 (5%)

Patients treated with Optune/TMZ experienced a small increase in TMZ-related AEs and SAEs due to the longer TMZ exposure afforded to these patient by their longer PFS. The only AEs which may have been caused by Optune therapy are the known skin irritation seen in 45% of patients in this study (1% severe), falls which were seen at a slightly higher incidence in patients carrying the device, headaches related to wearing the arrays 24 hours a day and mild psychiatric symptoms (anxiety, insomnia, confusion) which could be caused by the need to incorporate the device and arrays into daily life. No SAEs were considered related to device use. The remainder of AEs and SAEs seen in the trial were well balanced between treatment arms. In conclusion, Optune is very well tolerated with mild to moderate toxicity mainly related to array contact with the scalp.

Conclusions: Optune is a portable, battery operated device which delivers TFields to patients with recurrent diagnosed GBM. The results of the pivotal trial in newly diagnosed GBM showed that Optune/TMZ extends progression free and overall survival significantly compared to patients receiving TMZ alone. No significant increase in adverse events is seen when Optune treatment is added to TMZ. The only common device-related AE was a skin irritation seen beneath the transducer arrays in 45% percent of patients. The majority (44 of 45%) of these events were mild to moderate. Based on an assessment of the Quality of life of the interim analysis cohort of 315 patients, cognitive function and functional status did not decline due to the use of Optune/TMZ.

RECURRENT DIAGNOSED GLIOBLASTOMA

Pilot Clinical Study in Recurrent GBM

Optune has been tested in 10 recurrent GBM subjects in a single center, pilot study in Europe. In this study, Optune monotherapy led to a significant increase in time to progression (from 13 to 26 weeks; $p=0.013$), progression free survival at 6 months (PFS6) (from 15 to 50%) and overall survival (OS) (from 6.0 to 14.7 months; $p=0.002$) compared to matched concomitant and historical comparator groups. The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device transducer arrays.

Other Clinical Experience in Recurrent GBM

The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received Optune in a real-world, clinical practice setting in the US between 2011 and 2013. The registry included 457 recurrent GBM patients who received Optune in 91 US cancer centers. More patients in PRiDe than the pivotal clinical trial in recurrent GBM (EF-11) received Optune for first recurrence (33% vs. 9%) and had received prior bevacizumab therapy (55.1% vs. 19%). Median OS was significantly longer with Optune in clinical practice (PRiDe data set) than in the EF-11 pivotal trial in recurrent GBM (9.6 vs. 6.6 months). One- and 2-year OS rates were more than double for NovoTTF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% vs. 20%; 2-year: 30% vs. 9%). Favorable prognostic factors included first and second vs. third and subsequent recurrences, high Karnofsky Performance Score (KPS) and no prior bevacizumab use. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the Optune transducer arrays.

Pivotal Clinical Study in Recurrent GBM¹

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with Optune to those treated with an effective best standard of care (BSC) chemotherapy (including bevacizumab).

The following were the objectives of the study:

- To prospectively compare the median overall survival of recurrent GBM subjects treated with Optune to those treated with best standard of care (BSC) active chemotherapy
- To prospectively determine PFS6, TTP, %1-year survival and quality of life of subjects treated with Optune compared to BSC.
- To collect evidence of the safety of TTFields applied to subjects with recurrent GBM using Optune.

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows:

Inclusion Criteria

- a. Pathological evidence of GBM using WHO classification criteria
- b. ≥ 18 years of age
- c. Not a candidate for further radiotherapy or additional resection of residual tumor
- d. Subjects with disease progression (by Macdonald criteria (i.e., $> 25\%$ or new lesion)) documented by CT or MRI within 4 weeks prior to enrollment
- e. Karnofsky scale ≥ 70
- f. Life expectancy at least 3 months
- g. Participants of childbearing age must use effective contraception
- h. All subjects must sign written informed consent

Exclusion Criteria

- a. Actively participating in another clinical treatment trial
- b. Within 4 weeks from surgery for recurrence
- c. Within 4 weeks from any prior chemotherapy
- d. Within 4 weeks from radiation therapy
- e. Pregnant
- f. Significant co-morbidities within 4 weeks prior to enrollment:
 - 1) Significant liver function impairment AST or ALT > 3 times the upper limit of normal
 - 2) Total bilirubin $>$ upper limit of normal
 - 3) Significant renal impairment (serum creatinine > 1.7 mg/dL)
 - 4) Coagulopathy (as evidenced by PT or APTT > 1.5 times control in subjects not undergoing anticoagulation)
 - 5) Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
 - 6) Neutropenia (absolute neutrophil count $< 1 \times 10^3/\mu\text{L}$)
 - 7) Anemia (Hb < 10 g/L)
 - 8) Severe acute infection
- g. Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias
- h. Infra-tentorial tumor
- i. Evidence of increased intracranial pressure (midline shift > 5 mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

Study Procedures:

Treatment Arm

At treatment initiation subjects were hospitalized for 24 hours. During this period baseline examinations were performed and Optune treatment was initiated by the investigator under continuous medical supervision. The subjects were also instructed by the investigator on the operation of Optune and battery replacement. Once the subjects were trained in operating the device they were released to continue treatment at home. The subjects received continuous Optune treatment. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Subjects received the best effective standard of care chemotherapy practiced at each of the participating centers. The effective BSC treatments used in the study were comprised mainly of the following chemotherapies: Platinum based chemotherapy (Carboplatin), Nitrosureas (BCNU), Procarbazine, lomustine and vincristine (PCV), TMZ, Bevacizumab, and Imatinib, erlotinib, Irinotecan (mainly in Europe). Because these therapies were included in the trial as a group, no comparisons can be made to each individual chemotherapy regimen. Chemotherapeutic treatment protocol was according to standard procedures at each of the participating centers.

Follow-up

During treatment, and until progression for subjects who stopped treatment before progression, all subjects were seen once a month at an outpatient clinic where they underwent medical follow up and routine laboratory exams. An MRI was performed every 2 months until disease progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each subject. Medical follow-up continued for 2 months following disease progression. Subject survival was assessed based on monthly telephone interviews with the subjects' caregivers.

Subject Characteristics: 237 subjects (120 Optune; 117 BSC) with progressive or recurrent GBM were enrolled in the study. Baseline characteristics were as follows: mean age: 53.6 years; mean Karnofsky score: $81.6 \pm 10.9\%$; tumor size (cm^3): 16.2 ± 12.4 ; progression number: 1.4 ± 0.9 ; re-operated: 26%; male: 70%; previous low grade: 10%; prior bevacizumab failure: 19%. Baseline characteristics were similar between treatment groups with slightly more men in the Optune group than in the BSC group (77% vs. 62%), a lower incidence of frontal lobe tumors in the Optune group than in the BSC group (32% vs. 50%), and a slightly higher mean KPS in the Optune group than in the BSC group (83% vs. 80%), though the median KPS was 80 in both groups. Adjusted analyses for all pre-specified or all statistically significant baseline covariates for overall survival did not change the outcome of the trial.

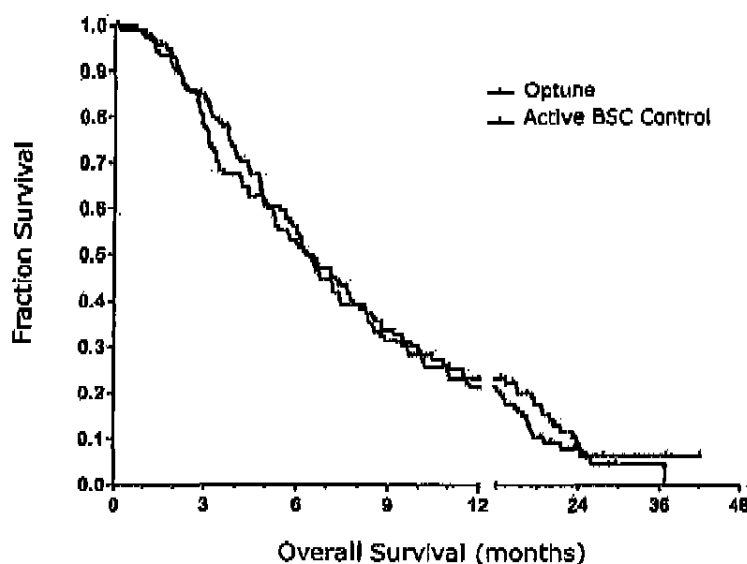
Demographic and Baseline Characteristics (mm)		
	Optune	BSC
Characteristics	(N=120)	(N=117)
	n (%)	n (%)
Caucasian	111 (93)	106 (91)
African American	2 (2)	5 (4)
Asian	0	3 (3)
Hispanic	7 (6)	2 (2)
Other	0	1 (1)
Female Gender	28 (23)	44 (38)
Frontal Tumor Position	38 (32)	58 (50)
Bilateral or Midline Tumor Location	23 (19)	17 (15)
Prior Avastin Use	24 (20)	21 (18)
Re-operation for Recurrence	33 (28)	29 (25)
Prior Low-grade Glioma	12 (10)	11 (9)
Median Age (years) (min, max)	54 (24, 80)	54 (29, 74)
Median Weight (kg)	80	80
Mean Number of Prior GBM Recurrences	1.5	1.3
Median Karnofsky Performance Score (min, max)	88 (50, 100)	80 (50, 100)
Median Tumor Area (mm^2)	1440	1391
Median Time from GBM Diagnosis to Randomization (days)	334	340
Mean Time from Last Radiotherapy Dose to Randomization (Months)	13.71	13.93

Effectiveness Results:**Primary Effectiveness Endpoint: Overall Survival (ITT)**

In the ITT population which included all randomized subjects (Novo-TTF=120, BSC=117), overall survival in subjects treated with Optune was comparable to that observed in subjects treated with BSC (median OS=6.3 vs. 6.4 months; p=0.98). In the US, the median overall survival was 6.1 vs. 5.3 months in the ITT population. The pivotal study data establish that Optune therapy is comparable to BSC therapy in extending OS.

	Treatment Group	
	Optune	BSC
N	120	117
Median OS (months)	6.3	6.4
Log-rank p-Value	0.98	
Hazard Ratio (95% CI)	1.00 (0.76-1.32)	

The Kaplan-Meier survival curve for the two treatment groups appeared to be very similar during the first 12 months of follow-up, where 80% of the events occurred in both groups. Between 12 and 24 months, the survival curves separated slightly in favor of the BSC control group. However, after 12 months, the number of subjects remaining may be too small to reliably estimate the long term survival outcome.



	Optune (N=120)	Active BSC Control (N=117)
Deaths	105	97
Censored	15	20
Lost to follow-up	6	10
Alive at end of follow-up	9	10
Median (months)	6.3	6.4
95% Confidence Interval	5.6, 7.8	5.2, 7.4

Correlation between Treatment Compliance and Overall Survival: Optune has an internal log file which allows the calculation of patient compliance with treatment. Significantly higher overall survival ($p=0.0447$) was observed in patients who were treated 75% or more of the time on average (OS=7.7 months) compared to patients treated less than 75% of the time on average (OS=4.5 months).

Secondary Effectiveness Endpoints: Secondary endpoint results support the findings in the primary endpoint. The one-year survival is similar in the Optune and BSC groups in the ITT population (21.9% vs. 22.1%). Progression free survival at 6 months (PFS6) is the same in the ITT population (21.4% vs. 15.2%). Radiological response rates from the subset of patients evaluated were reported as 14% for the Optune group compared to 9.6% for the BSC group in the ITT population. Median time to progression (TTP) was 9.3 weeks for Optune vs. 9.6 weeks for BSC.

	Treatment Group	
	Optune	BSC
N	120	117
1-year survival	21.9% 25/114	22.1% 23/104
PFS6 (%)	21.4% 22/103	15.2% 14/92
Radiological Response Rate (%)	14.0% 14/100	9.6% 7/73
Median TTP (weeks)	9.3	9.6

Quality of Life: Quality of life in subjects using Optune was better than those on BSC chemotherapy in most subscale domains, including vomiting, nausea, pain, diarrhea, constipation, cognitive and emotional functioning.

Safety Results: The characteristic adverse events of almost all chemotherapies are seen in a significantly higher proportion of BSC control subjects than in Optune subjects: gastrointestinal (30% vs. 8%), hematological (19% vs. 4%) and infectious (12% vs. 4%). Mild to moderate skin irritation beneath the device transducer arrays was observed in 16% of Optune subjects; none of these cases were assessed as severe by the investigator, all resolved after discontinuing treatment, and all were treated with topical steroids and periodic shifting of transducer array positions.

Number of Patients with Adverse Events by Body System (>2%)

Adverse Event Category	Optune	BSC chemotherapy
	N (%)	N (%)
Blood and lymphatic disorders	5 (4.3%)	17 (18.7%)
Gastrointestinal disorders	9 (7.8%)	27 (29.7%)
General disorders and administration site conditions	15 (12.9%)	14 (15.4%)
Infections and infestations	5 (4.3%)	11 (12.1%)
Injury, poisoning and procedural complications	21 (18.1%)	1 (1.1%)
Metabolism and nutrition disorders	9 (7.8%)	12 (13.2%)
Nervous system disorders	50 (43.1%)	33 (36.3%)
Psychiatric disorders	12 (10.3%)	7 (7.7%)
Respiratory, thoracic and mediastinal disorders	7 (6.0%)	10 (11.0%)

Conclusions: Optune is a portable, battery operated device which delivers TTFields to patients with recurrent GBM. The results of the pivotal trial showed that Optune subjects had comparable overall survival to subjects receiving the best available chemotherapy in the US today (OS 6.3 vs. 6.4 months; HR 1.0; p=0.98). Similar results showing comparability of Optune to BSC chemotherapy in the ITT population were seen in all secondary endpoints.

Optune subjects experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to BSC controls. The only device-related adverse event seen was a mild to moderate skin irritation beneath the device transducer arrays, which was easily treated with topical ointments. Finally, certain quality of life measures were better in Optune subjects as a group when compared to subjects receiving effective BSC chemotherapy.

Directions for Use

Detailed directions for use for Optune can be found in:
The Optune Patient Information and Operation Manual

Abbreviations

AE – Adverse event

BSC – Best standard of care (effective chemotherapies)

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor

ITT – Intent-to-Treat. This analysis population includes all randomized subjects.

kHz – kilo hertz; number of cycles per second

Optune– A portable battery, or power supply, operated device for delivering 200 kHz TTFields to the brain of patients with recurrent GBM

OS – Overall survival

PP – Per Protocol. This analysis population includes all patients who received at least the first course of TMZ and had no major protocol deviations.

PFS – Progression free survival

PFS6 – Proportion of patients alive and progression free at 6 months from randomization

Radiological Response Rate – sum of complete and partial radiological response rates

TMZ – a type of cancer drug used to treat newly diagnosed GBM

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body afflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

TTP – Time to progression

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

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The following abstract will be presented on Saturday, November 15, 2014, at 11:40am at the 19th Annual Scientific Meeting of the Society for Neuro-Oncology. The information below is embargoed until 8:00am, Saturday, November 15, 2014.

Interim Analysis of the EF-14 Trial: A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM

Roger Stupp, Eric Wong, Charles Scott, Sophie Tallibert, Andrew Kanner, Santosh Kesari and Zvi Ram on behalf of the EF-14 Trial Investigators

BACKGROUND: Tumor Treating Fields (TTFields) are an anti-mitotic, physical treatment modality that acts in metaphase, anaphase and telophase. The NovoTTF-100A System (NovoTTF), a home-use medical device that delivers TTFields to the brain, is an established monotherapy for recurrent glioblastoma (GBM).

METHODS: We conducted an international, multicenter, prospective, randomized phase III trial in newly diagnosed GBM patients. After completion of radiotherapy (RT) with concomitant temozolomide (TMZ), patients were randomized (2:1) to adjuvant TMZ with NovoTTF or adjuvant TMZ alone. The primary endpoint was progression-free survival (PFS), with overall survival (OS) an important secondary endpoint. Here we report on a pre-specified interim analysis of the first 315 patients randomized, after a minimum follow-up of 18 months (range 18-60 months).

RESULTS: (Intent-to-treat): 210 pts were randomized to NovoTTF/TMZ and 105 to TMZ alone. Patient characteristics were balanced: median age 57 and 58 years, tumor resection in 89 and 90%, KPS 90%, for the NovoTTF and the control arms, respectively. MGMT promoter methylation status was assessable centrally in 60% of patients; of these 39% and 41% were methylated. Adverse events (AE) were comparable between treatment arms. The most common device-related AE was skin irritation in 45% of patients (all grades, severe 2%). Severe seizures were observed at a frequency of 7% in both arms. Median PFS was 7.1 months [mo] [95% confidence interval [CI] 5.9-8.2] and 4.0 mo [CI 3.0-4.3; Hazard ratio 0.63, $p=0.001$], OS was 19.6 mo [CI 16.5-24.1] and 16.6 mo [CI 13.5-19.1] (HR 0.75, $p=0.034$), both favoring NovoTTF. This translates into a 24-mo survival rate of 43% (CI 36-50%) and 29% (CI 21-39%) for the NovoTTF/TMZ and the TMZ alone arm, respectively.

CONCLUSIONS: The trial met its primary and main secondary endpoints, and was closed to accrual after this interim analysis. Adjuvant TMZ chemotherapy and NovoTTF provides a clinically and statistically significant improvement in progression-free and overall survival, and should become the new standard of care against GBM.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C5-08-27
Baltimore, Maryland 21244-1850



Center for Medicare

Refer to: FCHBE

JUL 26 2013

James C. Stansel
Sidley Austin LLP
1501 K Street, NW
Washington, DC 20005

Dear Mr. Stansel:

Thank you for your inquiry requesting an informal benefit category determination (BCD) for the NovoTTFTM-100A System.

According to your letter and the information you provided during the meeting with Centers for Medicare and Medicaid Services (CMS) on May 21, 2013, the NovoTTFTM-100A System is a non-invasive system used in the patient's home that delivers tumor treating fields therapy to the brain to disrupt rapid cell division exhibited by recurrent GBM tumors. The NovoTTFTM-100A System is comprised of a durable electrical field generator and disposable insulated transducer arrays for use with the Generator. The System also includes lithium ion batteries, battery rack, battery charger, power supply, connection cables, and a carrying case. The NovoTTFTM-100A System received pre-market approval (PMA) from FDA in April 2011 for recurrent GBM.

In order for an item to be covered by Medicare, it must meet the definition of a Medicare-covered benefit. However, it is important to note that although Medicare provides coverage for certain items, it does not provide coverage for every item that may be useful to a person with a medical problem, even if a physician prescribes the item. The Medicare definition of durable medical equipment (DME) includes equipment which: can withstand repeated use; has an expected life of at least three years; is primarily and customarily used to serve a medical purpose; generally is not useful to a person in the absence of an illness or injury; and is appropriate for use in the home.

Based on the product information we reviewed, we believe that the NovoTTFTM-100A System falls within the DME benefit category. I hope that this information is helpful to you.

Sincerely,

A handwritten signature in dark ink, appearing to read "Joel E. Kaiser".

Joel E. Kaiser
Director

Division of DMEPOS Policy



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room - WO66-G609
Silver Spring, MD 20993-0002

NovoCure, Ltd.
% Mr. Jonathan S. Kahan
Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, N.W.
Washington, D.C. 20004

APR 8 2011

Re: P100034
NovoTTR-100A System
Filed: August 16, 2010
Amended: September 10, October 19, December 13, and December 27, 2011; and
February 17, and April 8, 2011
Procoda: NZK

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the NovoTTR-100A System. This device is indicated for treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme, following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(g) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Page 2 - Mr. Jonathan S. Kahan

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the conditions outline above, you must conduct the following post-approval study (PAS):

The New Enrollment Study for NovoTTF-100A in Recurrent GBM Patients: Per agreed on study outline (e-mail dated April 5, 2011) this study will address the following question: Is the overall survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)? This question will be addressed with a prospective, multi-center, non-randomized, unblinded, concurrent control study of NovoTTF-100A in recurrent Glioblastoma Multiforme (GBM) patients. The study will be conducted in at least 30 sites, at least half of them in the United States, and may include centers with previous experience with the device. Patients 22 years old and older will be included in the PAS. A total of 486 subjects will be enrolled, with 243 subjects per study arm. All study participants will be followed until death. Study follow-up visits include baseline and monthly in-office visits until disease progression. Assessment at baseline includes the Mini Mental State Examination (MMSE) and genetic profiling. The monthly assessments include survival status, MMSE and adverse events assessment. After disease progression study participants will be followed by monthly phone calls to determine survival status.

The primary data analysis will compare overall survival in NovoTTF-100A patients to that seen in concurrent BSC comparison patients, in the investigational device exemption (IDE) study Intent-to-Treat population, within a predefined confidence interval bound consistent with a performance goal of 1.375. The secondary endpoints will be: Change in neuro-cognitive function from baseline based on the MMSE; Genetic profiling of tumors and correlation with response to NovoTTF-100A treatment, specifically:

- MGMT promoter methylation status
- EGFR amplification, over expression or rearrangement
- Chromosomes 1p/19q deletion status
- Adverse event incidence by body system and term, including:
- Incidence of seizures
- Anticonvulsant use

Page 3 - Mr. Jonathan S. Kahan

Please be advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

In addition to the Annual Report requirements, FDA would like to remind you that you are required to submit PAS Progress Reports every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order"

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm>

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order"

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process"

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082274.htm

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

Page 4 - Mr. Jonathan S. Kahan

device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportsProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

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Page 5 - Mr. Jonathan S. Kahan

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information:


<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/howtoMarketYourDevice/PreMarketSubmissions/ucm134508.htm>; clinical and statistical data:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/howtoMarketYourDevice/PreMarketSubmissions/ucm134377.htm>)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center -- WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Ms. Jan C. Callaway at 301-796-5620.

Sincerely yours,



Christy Foreman
Acting Director
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

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NOVOTTF-100A SYSTEM

PRODUCT DOSSIER

FDA Approved Treatment for Recurrent Glioblastoma Multiforme

US FDA Pre-Market Approval (PMA) P100034

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List of Abbreviations and Definitions of Terms

AE – Adverse Event

ALT – Alanine Transaminase

APTT – Activate Partial Thromboplastin Time

AST – Aspartate Transaminase

B16F1 – Type of melanoma cells

BCNU – Carmustine, chemotherapy

CHEMOTHERAPY – Best Standard of Care (effective chemotherapies)

C – Centigrade

CCNU – Lomustine (CeeNU), chemotherapy

CNS – Central Nervous System

CRF – Case Report Form

ECG – Electrocardiogram

EMC – Electromagnetic Compatibility

F-98 – Rat glioblastoma cell line

FDA – Food and Drug Administration

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor.

Gy – Gray, unit of radiation

Hb – Hemoglobin

ITT – Intent-to-Treat

INE – Insulated Electrical Array

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kHz – Kilo Hertz; number of cycles per second

KPS – Karnofsky Scale

Ltd. – Private limited company

mA – Measure of electrical current

mg/dL – Milligrams per deciliter

mm – Millimeter

mm² – Millimeter squared

MHz – Mega Hertz, number of cycles per second

MRI – Magnetic Resonance Imaging

NSCLC – Non-Small Cell Lung Cancer

NovoTTF-100A System – A portable battery, or power supply, operated device for delivering 200 kHz TTFIELDS to the brain of patients with recurrent GBM.

• Abbreviated in this document as the NovoTTF device

OS – Overall Survival

OUS – Outside United States

p-value – Probability Value

PCV – Procarbazine, CCNU and vincristine-combination chemotherapy

PFS6 – Progression Free Survival at 6 months

PMA – Pre-market Approval

PT – Prothrombin Time

QOL – Quality of Life

QLQ C30 – Questionnaire developed to assess the quality of life of cancer patients

Radiological Response Rate or RR – Sum of complete and partial radiological response rates

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RMS – Root Mean Square; a measure of the intensity of a sinusoidal waveform

RT Dose – Radiation dose

SAEs – Serious Adverse Events

TENS – Transcutaneous Electrical Nerve Stimulation

TTFs – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body afflicted with a solid tumor. The fields have been shown to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase.

TTF Therapy – treatment using Tumor Treating Fields

TTP – Time to Progression

uL – Microliter

U-87 – Human glioblastoma cell line

US – United States

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

WHO – World Health Organization

95% CI – 95% Confidence level

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Executive Summary

Introduction

The NovoTTF-100A System (the "NovoTTF") is a portable, wearable medical device that delivers tumor treating fields ("TTFs") therapy ("TTF therapy") to a targeted tumor. Patients maintain normal daily activities while receiving TTF therapy continuously. The FDA has approved the device as a treatment for recurrent glioblastoma multiforme ("GBM") brain tumors.

FDA Approval

The US Food and Drug Administration (FDA) approved the NovoTTF-100A System under the pre-market approval (PMA) pathway in April 2011. The PMA approval pathway is the most rigorous medical device approval pathway and is analogous to the FDA new drug application (NDA) pathway. The FDA approved the device on the basis of results from a multi-center randomized controlled pivotal (phase III) clinical trial. The FDA PMA approval followed a positive vote from the FDA's Independent Medical Device Advisory Committee's Neurological Devices Panel. (See FDA Approval Letter, Appendix A.)

Indication for Use: The NovoTTF-100A is intended as a treatment for adult patients [22 years of age or older] with histologically-confirmed glioblastoma multiforme [GBM], following histologically- or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Glioblastoma Disease & Population Estimates

Glioblastoma multiforme (GBM, WHO Astrocytoma grade IV) although considered the most common form of primary brain tumor is a rare disease. GBM is universally fatal and the disease is classified as "recurrent GBM" when the tumor recurs or progresses after standard treatment. Patients with recurrent GBM have a one-year survival rate of approximately 10% and a median overall survival time of 3 to 5 months when not treated with an effective (active) therapy.

Glioblastoma affects approximately 10,000 people annually in the US, of which fewer than 7,000 will likely seek treatment for recurrent GBM. The median age at diagnosis is approximately 64 years and approximately 65 percent of patients are under 65 years of age. The expected population for a private health care payer in the US is approximately 16 patients per 1 million covered lives (7,000 x 65% non Medicare x 70% with private health care coverage).

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Glioblastoma Current Standard of Care

At diagnosis patients with GBM undergo debulking surgery, if possible, followed by concomitant radiotherapy and chemotherapy using temozolomide (Merck; Temodar). Some patients have carmustine wafers (Gliadel Wafers) implanted in the resection cavity at the time of surgery. This initial treatment is then followed by monthly courses of temozolomide which are repeated for six months or until disease progression.

When the disease relapses (recurrent GBM) treatment options are limited. Only 20% of recurrent GBM patients are candidates for additional debulking surgery, with or without Gliadel Wafer placement, at the time of recurrence. A small number of patients can receive an ionizing radiation boost to the area of recurrence.

Most recurrent glioblastoma patients in the US are treated with bevacizumab (Avastin), or experimental treatments. Bevacizumab is the only chemotherapy specifically approved by FDA for recurrent glioblastoma. The FDA approved bevacizumab for this indication on the basis of data from a non-randomized trial. Bevacizumab for recurrent glioblastoma has not been demonstrated to extend overall survival versus a control group.

Scientific Basis of TTF Therapy

Tumor treating fields therapy (TTF therapy) is an electric field based loco-regional, antimitotic treatment modality, which has been shown to inhibit the growth of cancerous tumors *in vitro* and *in vivo*. TTF therapy has been shown to:

- inhibit cancer cell replication by interference with the proper formation of the mitotic spindle during anaphase; and
- cause intracellular dislocation of macromolecule and organelles during late telophase.

Acting together, these two processes, which are specific to dividing cells only, lead to apoptosis and can result in tumor arrest or regression *in vivo*. Most healthy adult brain cells proliferate very slowly, if at all, and are thus not affected by the TTFields. Additionally, the antimitotic effect of TTF therapy has been shown to be frequency-specific to the cell type treated. Specifically, TTFields that inhibit the replication of GBM tumor cells do not affect the replication of other cell types (e.g., neurons), nor do they affect neuronal function.

TTFields are intermediate frequency (200 kHz) and low intensity (1-3 V/cm) alternating electric fields. At this frequency and intensity, TTFields cannot stimulate nerves or muscles, nor do they lead to heating of the tumor or surrounding tissues. Since TTFields are applied using electrically insulated arrays, there is no direct current flow into the tissue so that electrolysis and tissue damage do not occur over time.

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Product Description

The NovoTTF-100A System is a prescription only device that is intended for continuous use throughout the day by the patient. The NovoTTF is comprised of two main components: 1) an Electric Field Generator (the device) and 2) INE Insulated Transducer Arrays. The device delivers TFields to the patient through four electrically-insulated, disposable, surface transducer arrays placed on the patient's shaved scalp. The NovoTTF-100A System also contains a power supply, portable batteries, battery rack, battery charger, connection cable and carrying case. (See Figure 1 for illustration of components.)

Device Use

The treating physician must complete training and receive certification from the manufacturer prior to prescribing the treatment. Additionally, nurses, nurse practitioners, physician's assistants and any other health care professional providing direct patient care related to the NovoTTF-100A System must also have completed training and certification.

Prior to starting treatment the physician plans the appropriate layout of transducer arrays around the tumor location. The patient then has their scalp shaved to ensure proper contact of the transducer array to the skin. The physician then places the arrays (or provides supervision to a nurse or PA) on the patient's scalp in accordance with the layout plan. The physician then directly initiates treatment by turning the machine on and ensures safe treatment start. The physician and/or nurse trains the patient and the caregivers on proper use of the system including battery charging and replacement, transducer array replacement and problem solving procedures.

The INE Insulated Transducer Arrays (the "Arrays") are disposable and approved for single use only. The Arrays are removed, the scalp re-shaved, and new Arrays are placed as hair grows back, typically every 2 to 3 days. The Arrays are highly engineered and designed to deliver and monitor the therapy simultaneously, while maintaining electrical insulation and patient safety. Due to the advanced engineering requirements and their unique material composition, the Arrays will contribute meaningfully to the device cost.

The prescribing physician will likely require that patients return to their office for Array placements in the first two weeks after starting therapy, and as needed thereafter. The physician, during these visits, will be able to provide the patient with additional training and ensure that the Array placement is in accordance with the treatment plan. Once properly trained, the patient is expected to make Array placements at home with the assistance of caregiver. (See Figure 2 for illustration of device usage.)

The physician-prescribed device is used until clinical disease progression. The recommended average daily use is at least 18 hours a day. The median duration of treatment with the NovoTTF was 2.4 months in the pivotal trial. Some patients in the

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pivotal trial were treated with the NovoTTF for greater than one year, which reflects that fact that the device produced durable tumor responses in certain patients.

EF-11 Pivotal Trial for the NovoTTF-100A System

The FDA approved the NovoTTF on the basis of a multicenter, randomized, controlled clinical trial that enrolled 237 patients. The study design:

- evaluated the safety and effectiveness of the NovoTTF as a monotherapy in the treatment of recurrent GBM,
- randomized patients in two arms: 1) NovoTTF alone, or 2) active chemotherapy selected by the physician (chemo), and
- enrolled patients with balanced characteristics between the two arms.

The chemotherapy treatments in the control arm were comprised mainly of the following chemotherapies: bevacizumab, temozolomide, platinum based chemotherapy (Carboplatin), nitrosureas (CCNU), procarbazine alone, procarbazine with lomustine and vincristine (PCV), and imatinib, erlotinib, irinotecan.

The primary efficacy endpoint for the trial was overall survival (OS). The secondary efficacy endpoints were one year survival rate, progression free survival rate at six months (PFS6), radiologic response rate, and quality of life (QOL).

The efficacy data was analyzed in an intent-to-treat (ITT) population that included all patients randomized to the trial. The efficacy data demonstrated that NovoTTF produces clinically comparable outcomes to chemotherapy in both primary and secondary endpoints with more radiographic responses and a higher PFS-6 seen in NovoTTF patients than chemotherapy patients (not statistically significant):

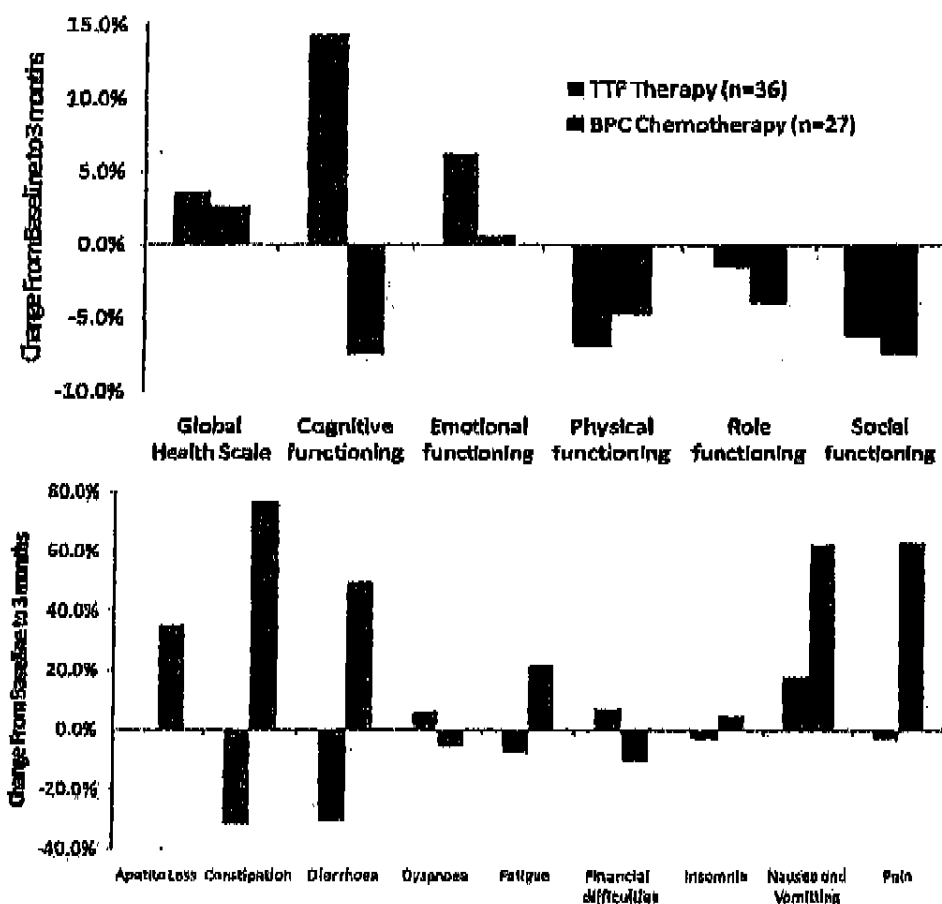
Table 1. Pivotal Trial Efficacy Results – Intent to Treat Population

Treatment Arm	Overall Survival	Radiographic Response Rate	1-year Survival%	PFS-6
NovoTTF	6.3 m	14%	22%	21%
Chemo	6.4 m	10%	22%	15%

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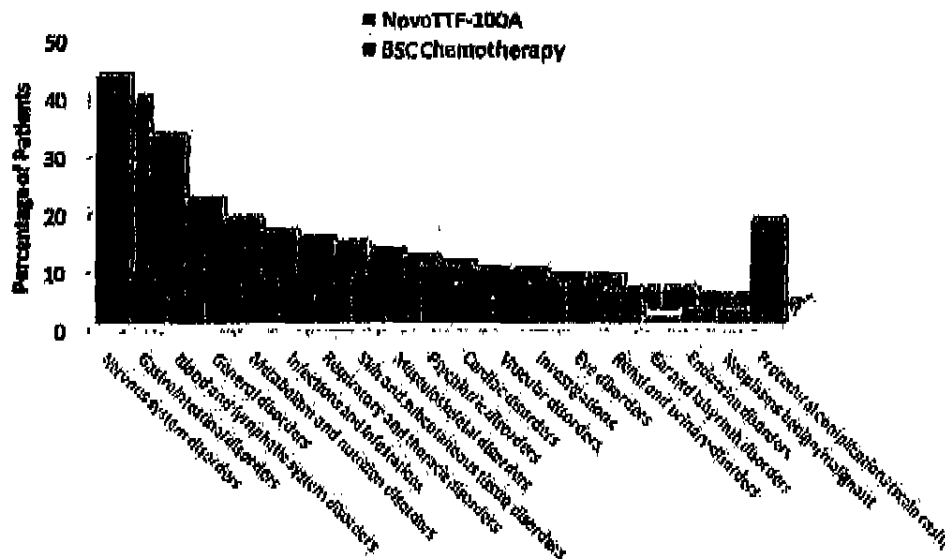
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Additionally, QOL based on validated questionnaires was consistently higher for NovoTTF-100A patients than for active chemotherapy patients in the following important domains: vomiting, nausea, pain, diarrhea, constipation, cognitive functioning and emotional functioning.



The primary safety endpoint was the safety and tolerability of the NovoTTF based on the incidence and severity of adverse events (AE) and toxicities. The NovoTTF-100A System was well tolerated by patients during the study as indicated by an average daily use of over 20 hours. Expected mild to moderate localized skin irritation on the scalp at the site of transducer array contact was observed. Patients in the active chemotherapy group, as anticipated, experienced significantly higher rates of chemotherapy-associated AEs e.g. hematological, gastrointestinal, and infectious AEs.

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Regulatory Approval Outside the United States

The manufacturer has applied the CE Mark to the device and received marketing approvals in the UK, Ireland, France, Germany, Italy, Greece and Switzerland for treatment of both recurrent and newly diagnosed GBM. The NovoTTF-100A System has been commercially available in the European Union since 2009.

About Novocure

Novocure Ltd., a private oncology company based in Europe, manufactures the NovoTTF. The device is marketed and distributed in the United States by Novocure (USA) Inc. of Portsmouth, NH (together "Novocure"), a wholly-owned subsidiary. Novocure is dedicated to the development of a novel, low toxicity, non-pharmaceutical cancer treatment modality that will positively impact patient survival while maintaining a high quality of life. Investors in the company include Johnson & Johnson Development Corporation (JJDC), Pfizer, Medtronic, Index Ventures and WFD Ventures.

Product Dossier Outline

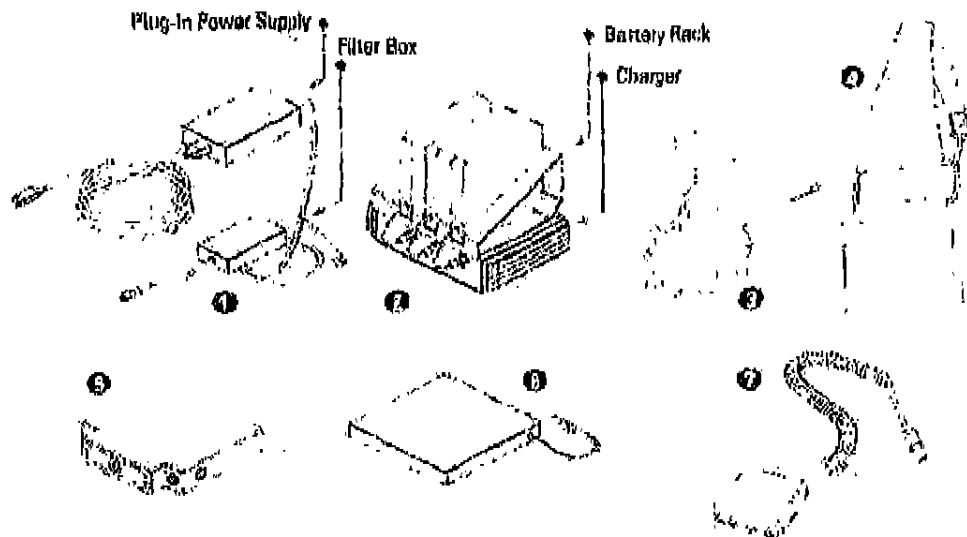
This NovoTTF-100A System dossier includes the following:

- 1] Burden of Illness and Standard of Care for GBM
- 2] Description and Use of the NovoTTF-100A System
- 3] NovoTTF-100A Mechanism of Action and Preclinical Data
- 4] Summary of Clinical Studies

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Figure 1. NovoTTF-100A System Components

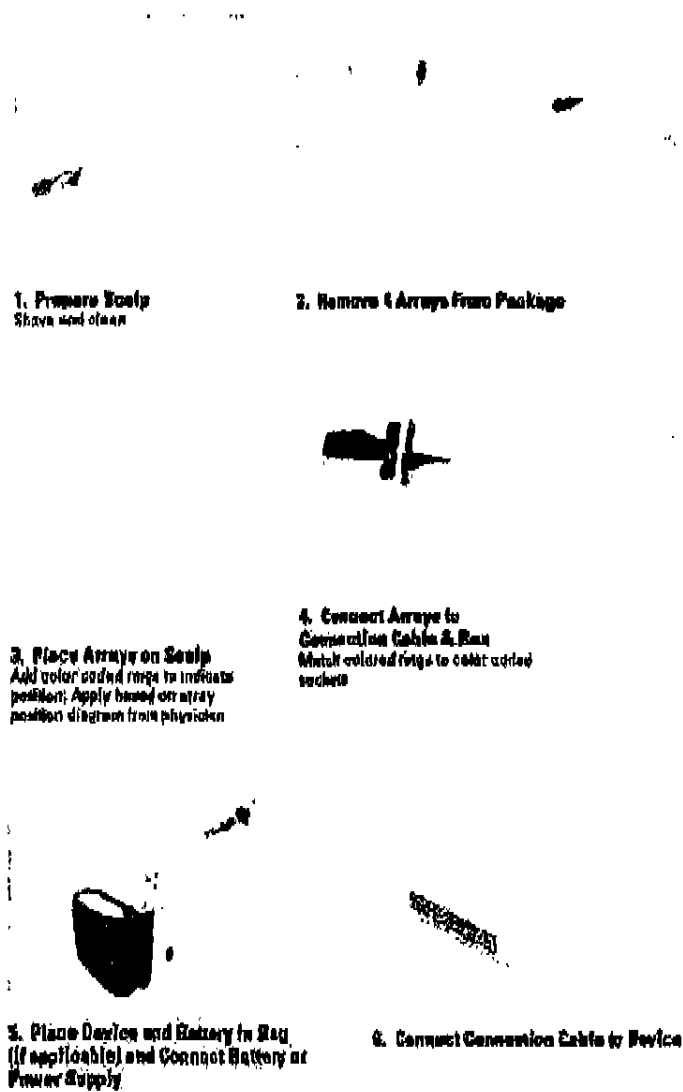


1. Plug in power supply
2. Charger for portable batteries
3. Transducer array
4. Device and battery carrying bag
5. NovoTTF-100A electric field generator (the Device)
6. Portable battery
7. Connection cable

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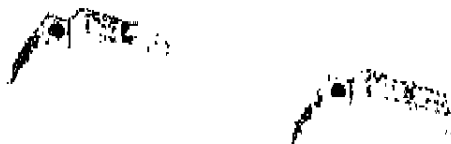
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Figure 2. Use of Device Overview



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2. Start Treatment!
Turn on power supply and push "Treat" button



3. Place Bag Over Shoulder and Clip
Hinge

4. Repose Arm as Needed
5. Repose Shoulder When Not in Use

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1) Burden of Illness and Standard of Care for GBM

Glioblastoma, a malignant form of astrocytoma, is the most common form of primary brain cancer.

Burden of Illness

The incidence of GBM increases steadily above 45 years of age with approximately 10,000 new cases annually in the United States. GBM tends to occur more frequently in males than females by a ratio of about 3:2. The outcome of patients with this disease has not improved significantly in the past decade, despite the introduction of improved chemotherapies, including temozolomide (Merck; Temodar), bevacizumab (Roche; Avastin), and the use of Gliadel Wafers (carmustine). The 4-year survival of these patients is only 12%, with a median overall survival of 14.7 months (Stupp, 2005). Thus, with optimal therapy, OS of these patients currently is less than 15 months from initial diagnosis.

Recurrent GBM is an end-stage condition; it is uniformly fatal with a 1-year survival of about 10%. Overall survival from time of recurrence is approximately 3 to 5 months without additional effective treatment. QOL for patients with recurrent GBM is poor due to the neurological deficits caused by the tumor itself together with the overwhelming side effects of the various standard chemotherapies and experimental treatments. Patients receiving chemotherapies suffer from wound healing complications, infections, diarrhea, constipation, nausea, vomiting, pain, decreased blood cell counts (and their complications), bleeding disorders and thromboembolic events (e.g., stroke).

Recurrent Glioblastoma Population Estimates

Glioblastoma affects approximately 10,000 people annually in the US, of which fewer than 7,000 will likely seek treatment for a recurrent GBM. This estimate is based on the fact that Stupp et al. (NEJM 2005) reported that 73% of glioblastoma patients had a recurrence in the first year.

The median age at diagnosis is approximately 54 years and approximately 65 percent of patients are under 65 years of age. Therefore, the expected population for a private health care payer in the US is approximately 16 patients per 1 million covered lives (7,000 x 65% non Medicare x 70% with private health care coverage = 3,185 divided by 196 million covered lives with private insurance = 16 lives per million covered).

Existing Treatment Options for Recurrent Glioblastoma

There are currently four principal treatment options for recurrent GBM, each with its own drawbacks and major side effects.

- **Surgical Resection** – The rate of re-operation for glioblastoma at the time of tumor recurrence was 20.5±12.8% (median ± standard deviation) in a recent

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review (Romanelli, 2009). The effect of reoperation on disease progression and survival is controversial. (Brandes, 1999)

- **GLIADEL® Wafer In Combination with Surgical Resection** – The Gliadel Wafer delivers carmustine (BCNU) directly to the site of the brain tumor (interstitial chemotherapy). It is indicated for newly diagnosed as well as recurrent GBM. The package insert indicates that for recurrent GBM, Gliadel increased median OS from 4.5 to 5.8 months compared to placebo. Unfortunately, this approach is limited to those selected cases undergoing surgical resection for GBM, as discussed above. It is also limited by significant toxicity and wound healing complications.

Treatment with the GLIADEL® Wafer is associated with the following common side effects: fever (12%), pain (8%), wound healing abnormalities (14%), nausea and vomiting (8%), seizures (19%), brain edema (4%) and intracranial infections (4%). (Brem, 1995)

- **Radiation Therapy** - The full standard dose of 60 gray (Gy) typically is given after initial diagnosis with glioblastoma such that irradiation for recurrence of the disease usually is not possible. However, focal radio-surgery upon recurrence of a small tumor in a single anatomic location may be possible. (Romanelli, 2009)

Side effects of radiation therapy depend on the type of radiation received, the amount of the surface of the brain targeted, the site targeted, and the total dose of radiation. In general, there will be hair loss, skin irritation, possible hearing problems, nausea, vomiting, loss of appetite and neurologic effects. The most prevalent side effect is fatigue, which may last through treatment and for many months afterwards. The neurological effects most affecting patients' QOL are permanent memory and speech problems. (Taphoorn, 2005)

- **Cytotoxic Chemotherapy** - There is no established standard treatment for recurrent GBM. Chemotherapy treatment strategies are ill-defined with several different regimens being used. The most common are: nitrosureas, (BCNU), procarbazine, PCV (procarbazine, CCNU and vincristine), and platinum based (e.g. carboplatin). None of these agents is FDA approved specifically for recurrent glioblastoma.

Treatment with chemotherapy commonly (in >30% of patients) causes leucopenia, anemia, nausea and vomiting, electrolyte disturbances, renal toxicity, pain or burning at administration site, redness of face, skin flushing (usually associated with rapid infusion rate of nitrosureas), loss of appetite, headache, fatigue and constipation. Thus, most patients suffer from

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combinations of unpleasant and sometimes life threatening side effects of their chemotherapeutic treatments. (DeVita, 2001)

More recently, bevacizumab (Avastin), a recombinant humanized monoclonal antibody, has been approved in the US as monotherapy for patients with previously treated GBM (Cohen, 2009) based on two single arm trials comparing bevacizumab to historical control data. Benefit was seen in radiological response rates and PFS6 compared to historical control data (based on the meta-analysis by Wong et al. (Wong, 1999) OS was shown to be between 8 to 9 months; (Friedman, 2009) however, an OS claim is not made in the approved labeling, noting the comparator arm was not a randomized control group.

In addition to the common chemotherapy side effects listed above, treatment with bevacizumab has other associated AEs, including gastrointestinal perforations, surgery and wound healing complications, hemorrhage (including brain hemorrhage), non-gastrointestinal fistula formation, arterial thromboembolic events, hypertensive crisis, reversible posterior leukoencephalopathy syndrome and proteinuria. (Avastin package insert and FDA Briefing Book, Avastin, 2009)

In summary, patients with recurrent glioblastoma have limited treatment options. Only 20% of patients are eligible for re-operation. Few patients are eligible for re-irradiation. And no gold standard for chemotherapy treatment is available at recurrence. The majority of the agents used by physicians are older generation chemotherapy products. These products have significant risk for adverse events and are not approved by FDA for use specifically in this indication. Finally, bevacizumab (Avastin), while approved for this indication by FDA, has never demonstrated a survival versus a control group.

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2] Description and Use of NovoTTF-100A System

Overview

The NovoTTF-100A System ("NovoTTF") is a portable, wearable medical device which produces alternating electrical fields, tumor treating fields or "TTFs", within the brain by means of electrically-insulated surface transducer arrays placed on the scalp. The TTFs are believed to disrupt the rapid cell division exhibited by cancer cells. (Klison, 2004 and 2007)

***Indication for Use:** The NovoTTF-100A is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM), following histologically- or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.*

System Components

The NovoTTF-100A System is comprised of two main components: 1) an Electric Field Generator (the "Device") and 2) INE Insulated Transducer Arrays (the "Arrays"). (See Figure 1 for illustration.)

- The Electric Field Generator is a portable, battery- or power supply-operated device. The device is connected to two pairs of insulated transducer array sets, which are operated sequentially. The intensity of the field, the frequency of the waves, and the temperature of the transducer arrays are pre-set. The device and battery weigh about six pounds together.
- Two sets of INE Insulated Transducer Arrays ("Arrays") are connected to the Electric Field Generator. The Arrays are disposable and for single use only. The Arrays are removed, the scalp re-shaved, and new Arrays are placed as hair grows back, typically every 2 to 3 days. The Arrays should be replaced at a minimum every 7 days to ensure contact with the skin. The Arrays utilize proprietary technology to deliver and monitor the therapy and, due to their advanced engineering requirements and unique material composition, contribute meaningfully to the device cost.

Additional Components: In addition to the Electric Field Generator and INE Transducer Arrays the NovoTTF-100A System includes a power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

Treatment Overview

Overview

The US FDA requires that the treating physician must complete training and receive certification from the manufacturer prior to prescribing treatment with the NovoTTF-

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100A System. Additionally, nurses, nurse practitioners, physician's assistants and any other health care professional providing direct patient care related to the NovoTTF-100A System must also have completed training and certification.

The training conducted by the manufacturer is designed to educate the prescribing physician on the scientific basis for TTF therapy, the process to interpret an MRI to determine the Array layout plan, the training required for the patient, and also the steps to start and oversee treatment, including the process of assessing monthly compliance.

Array Layout Plan

The physician must plan the appropriate layout of the Arrays around the tumor location prior to starting treatment. This layout planning process requires a current patient MRI and visual inspection of the patient's scalp. The physician determines the appropriate Array placement to maximize TTF intensity within the tumor.

Treatment Start

The patient then has their scalp shaved to ensure proper contact of the Arrays to the skin. The physician (or nurse under supervision) then places the arrays on the patient's scalp in accordance with the prescribed Array layout plan. The physician then confirms appropriate placement and the physician initiates the treatment by turning the Electric Field Generator on under his or her direct supervision.

Patient and Caregiver Training

The physician and his/her staff are responsible for training the patient and caregiver on the appropriate use of the device. This training includes technical training related to the device operation, including educating the patient on battery replacement, battery charging, using the power supply, connecting and disconnecting from the device and on the appropriate placement of Arrays in accordance with the treatment plan. The training also includes advice on proper skin care, as skin irritation at the treatment site is a known complication of the device. Additionally, the patient and caregiver will have access to a 24-hour technical support service offered by the device manufacturer.

Array Placements – Initial Period

The prescribing physician will likely require that patients return to the office for Array placements in the first two weeks after starting therapy, and as needed thereafter. The physician and his/her staff, during these visits, will be able to provide the patient with additional training. Based on clinical trial experience, it is likely that after the first 2 weeks the patient and caregiver will be able to manage Array replacements independently, without returning to the physician, in most cases.

Array Placements – After Successful Patient Training

The patient and caregiver, once properly trained, are expected to do the Array placements at home. The caregiver will be trained to shave the patient's scalp,

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maintain good skin care protocols, and to place the Arrays in accordance with the prescribed treatment plan.

Monthly Treatment Assessment

Recurrent glioblastoma patients are typically scheduled to meet the physician once per month, exclusive of NovoTTF treatment. The physician is trained and instructed to download a compliance log from the NovoTTF during this monthly appointment. The compliance log provides the physician with an overview of device usage by day and by time of day (day versus night). The physician is trained to use this compliance log to encourage appropriate use of the NovoTTF. During this monthly appointment the physician will also review the location of the Arrays to ensure appropriate placement in accordance with the prescribed treatment plan. If compliance is low, patients and caregivers may be retrained in the proper use of the device.

Device Use Overview

Treatment Time

The physician-prescribed device is used until clinical disease progression. The recommended average daily use is at least 18 hours a day. The median duration of treatment with the NovoTTF was 2.4 months in the pivotal trial. Some patients in the pivotal trial were treated with the NovoTTF for greater than one year, which reflects that fact that the device produced durable tumor responses in certain patients.

Device Settings

Novocure pre-sets all treatment parameters; there are no electrical output adjustments available to the patient. The patient simply connects the device to an appropriate power supply (i.e., a charged battery or connection of the power supply to an electrical outlet) and turns it on and off.

Practical Considerations

Treatment may be interrupted for personal needs such as bathing, exercise, or any situation in which the device may be a distraction. For example, in order to take a shower, the patient must disconnect from the device (leaving the Arrays on the head), put on a shower cap and be cautious not to get his/her head wet. Treatment also must be stopped to replace the Arrays. When leaving the house, patients can put a wig or hat over the Arrays, if desired.

Device Service

The Electric Field Generator and batteries requires frequent servicing. Novocure will provide the patient with access to replacements for these components (shipped on an overnight basis). For minor technical issues, an alarm will sound to notify the patient. The patient manual has a simple troubleshooting guide that addresses the most common problems that may arise. In addition, Novocure has around-the-clock technical support. Patients are encouraged to call the Novocure technical support telephone number with questions about operations or device function.

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Contraindications: The NovoTTF-100A System is contraindicated in patients with an active implanted medical device, a skull defect (such as, missing bone with no replacement), a shunt or bullet fragments. Further, it should not be used in patients known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) transducer arrays. The device should not be used for patients 21 years old or younger or those pregnant or hoping to get pregnant, as it has not been tested in these populations. Interruptions in treatment may lower response rate to treatment.

FDA Approval

The US Food and Drug Administration (FDA) approved the NovoTTF-100A System under the pre-market approval (PMA) pathway in April 2011. The PMA approval pathway is the most rigorous medical device approval pathway and is analogous to the FDA new drug application (NDA) pathway. The FDA approved the device on the basis of results from a multi-center randomized active controlled pivotal (phase III) trial. The FDA PMA approval followed a positive vote from the FDA's Independent Medical Device Advisory Committee's Neurological Devices Panel. (See FDA Approval Letter, Appendix A.)

Indication for Use: The NovoTTF-100A is intended as a treatment for adult patients [22 years of age or older] with histologically-confirmed glioblastoma multiforme [GBM], following histologically- or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

OUS Regulatory Approvals

The manufacturer has applied the CE Mark to the device and received marketing approvals in the UK, Ireland, France, Germany, Italy, Greece and Switzerland for treatment of both recurrent and newly diagnosed GBM. The NovoTTF-100A System has been commercially available in the European Union since 2009.

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3] NovoTTF-100A Mechanism of Action and Preclinical Data

Background

The NovoTTF-100A System delivers tumor treating fields (TTF) therapy to the tumor. TTF therapy is intended to disrupt cancer cell division utilizing the unique electrical and geometric properties of cells during the mitotic process.

Electric fields have traditionally been used in medicine in two different modes: 1) steady or low frequency electric fields (<1 kHz); and 2) high frequency alternating fields (>10 MHz). Steady or low frequency electric fields generate action potentials in excitable cells. These fields are used therapeutically in bone and soft tissue repair, pain control (TENS), and stimulation (neurologic or cardiac). In contrast, very high frequency alternating fields generate heat in the tissues by dielectric losses. Applications in therapeutic use include ablation, diathermy and hyperthermia.

In contrast, the NovoTTF-100A System uses intermediate frequency (200 kHz), low intensity (single volts per cm), alternating electric fields to achieve its therapeutic effect. These intermediate electric fields, known as TTFields, are delivered non-invasively to solid tumors through electrically insulated surface transducer arrays using the NovoTTF-100A device.

Mechanism of Action

TTF therapy targets two specific characteristics of cancer cells: the presence of electrically charged particles during mitosis and the geometrical shape of dividing cancer cells. TTFields have been shown to disrupt mitotic spindle microtubule assembly and to lead to dielectrophoretic dislocation of intracellular macromolecules and organelles during cytokinesis (Kirsch et al., 2004). These processes lead to physical disruption of the cell membrane and to programmed cell death (apoptosis).

In contrast, TTFields do not affect cells that are in stasis, that is, that are not dividing. Since most normal adult brain cells proliferate very slowly, if at all, scientists hypothesize that these cells are affected minimally by the TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. TTFields are only applied to the brain, and thus have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any clinically meaningful increase in tissue temperature.

These mechanisms of action are consistent with the extensive peer-reviewed research regarding the effects of TTFields. These results demonstrate both disruption of cancer cell division up to complete cessation of the process, as well as complete destruction of

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the dividing cancer cells. There is no direct current flow into the tissue so that electrolysis and tissue damage do not occur over time. Thus, TTField application has the advantage of being highly selective and is not expected to be associated with significant toxicity. (Kirson, 2004)

Preclinical Data

TTFields have been shown both *in vitro* and *in vivo* to inhibit cancer cell replication effectively without systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to effectively inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed), due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase. (Kirson, 2004)

Specifically, TTFields have been shown to inhibit glioblastoma cells *in vitro* and *in vivo* at a frequency of 200 kHz and an intensity of 0.7 V/cm RMS. Based on realistic finite element mesh simulations and direct measurements of TTFields intensity in experimental animals, and in the human brain, Novocure has concluded that effective TTField intensities can be generated in the brains of large animals and humans.

Extensive safety studies in healthy animals (mice, rats and rabbits) have shown that TTFields are not associated with significant systemic toxicities. Neither acute, nor chronic systemic toxicities were seen when TTFields were applied to the torso or head, at different frequencies (100-200 kHz), different intensities and for different periods of time. (Kirson, 2007)

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for the NovoTTF-100A system has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course most likely will lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

In summary the preclinical data demonstrate the following (See Appendix B for more detailed discussion of the preclinical data.):

- TTFields are a low toxicity, antimitotic physical treatment modality.
- Extensive *in vitro* and *in vivo* data consistently show a clear frequency and intensity dependent inhibition of mitosis and reversal of tumor growth.
- The NovoTTF-100A device generates effective TTField intensities within the brain.

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- **Preclinical data support tumor growth inhibition without damage to normal neuronal function or structure or any systemic toxicity**

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4) Summary of Clinical Studies

Pilot Study for Recurrent GBM

A European 10-patient pilot study initially evaluated the effectiveness and safety of the NovoTTF-100A System in the treatment of recurrent GBM. The study was an open-label prospective single arm study in which patients received treatment with the NovoTTF-100A System as a monotherapy without concurrent chemotherapy. Patients were followed for six months after disease progression. The median time to progression in the NovoTTF-100A subjects was 26 weeks compared to 9 weeks in historical control data (Wong et al., 1999). Overall survival was 14.7 months for NovoTTF-100A subjects compared to the 6 months expected for effective chemotherapy or Gliadel wafers. Response rate in the NovoTTF-100A treated subjects was 25%. The study demonstrated an excellent safety profile for the device and served as the basis for the design of the pivotal (phase III) clinical trial described below.

EF-11 Pivotal (phase III) Clinical Study in Recurrent GBM

Overview

The FDA approved the NovoTTF-100A System on the basis of results from the EF-11 pivotal trial. The EF-11 trial was a multicenter, randomized, active controlled clinical trial designed to evaluate the safety and effectiveness of NovoTTF-100A System in the treatment of recurrent GBM. The results from this trial were presented at ASCO 2010 (Stupp, 2010) and have been audited by the FDA and approved by FDA for inclusion in the Instructions for Use (IFU) for the device. (Stupp, 2010 and IFU 2011).

The EF-11 study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with NovoTTF (alone) to those treated with an effective (active) chemotherapy (including bevacizumab) selected by the treating physician.

The specific aims of the study were:

- To prospectively compare the OS of recurrent GBM patients treated with NovoTTF-100A to those treated with chemotherapy.
- To prospectively determine the percent one year survival rate, PFS6, median TTP, radiological response rate and QOL of patients treated with the NovoTTF-100A compared to chemotherapy.
- To collect evidence of the safety of TTF fields applied to patients with recurrent GBM using the NovoTTF-100A System.
- To compare the median OS of recurrent GBM patients treated with NovoTTF-100A to historical control data.

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Study Population

Patients with previously diagnosed GBM who had relapsed or progressed despite conventional therapy (surgery and chemo-radiotherapy followed by chemotherapy) were recruited into the study. A total of 237 patients were enrolled in the study from 28 clinical centers. (US-16; Europe-11; and Israel-1) (See Appendix C for trial sites.). This number of patients is approximately 3% of the entire US population of recurrent GBM patients. The maximum number of patients recruited at one site was 21 patients; less than 10% of the total number of patients in the study. Approximately 50% of the patients were enrolled at the US sites. The final study analysis compared 120 NovoTTF-100A patients with 117 chemotherapy patients.

NOTE: the large study size and use of a control group compare favorably to the trial for bevacizumab in recurrent GBM, which had only 167 patients and no control arm. (Avastin Package Insert). Also note, the EF-11 trial of the NovoTTF-100A System is largest randomized clinical trial ever completed in this disease indication.

Key eligibility criteria follow:

• Inclusion Criteria

- Pathological evidence of GBM using WHO classification criteria
- ≥ 18 years of age
- Not a candidate for further radiotherapy or additional resection of residual tumor
- Subjects with disease progression (by Macdonald criteria (i.e., $> 25\%$ or new lesion)) documented by CT or MRI within 4 weeks prior to enrollment
- Karnofsky scale ≥ 70
- Life expectancy at least 3 months
- Participants of childbearing age must use effective contraception
- All subjects must sign written informed consent

• Exclusion Criteria

- Actively participating in another clinical treatment trial
- Within 4 weeks from surgery for recurrence
- Within 4 weeks from any prior chemotherapy
- Within 4 weeks from radiation therapy
- Pregnant
- Significant co-morbidities within 4 weeks prior to enrollment:
 - Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
 - Total bilirubin $>$ upper limit of normal
 - Significant renal impairment (serum creatinine > 1.7 mg/dL)
 - Coagulopathy (as evidenced by PT or APTT > 1.5 times control in subjects not undergoing anticoagulation)

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- Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
- Neutropenia (absolute neutrophil count $< 1 \times 10^3/\mu\text{L}$)
- Anemia (Hb $< 10 \text{ g/L}$)
- Severe acute infection
- Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias.
- Infra-tentorial tumor
- Evidence of increased intracranial pressure (midline shift $> 5\text{mm}$, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

Study Procedures

Treatment Arm: At treatment initiation, baseline examinations were performed and the investigator initiated NovoTTF-100A treatment under continuous medical supervision. The investigator also instructed patients on the operation of the NovoTTF-100A System and battery replacement. The patients then received continuous NovoTTF-100A treatment at home. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm: All patients had baseline examinations performed prior to treatment initiation. Patients received chemotherapy practiced at each of the participating centers. The effective chemotherapy treatments used in the study comprised mainly of the following chemotherapies: Bevacizumab (Avastin), platinum based chemotherapy (carboplatin), Nitrosureas (BCNU), procarbazine, lomustine and vincristine (PCV), temozolomide, and imatinib, erlotinib, irinotecan (mainly in Europe).

Randomization and Blinding: Patients who met the eligibility criteria were randomized in a 1:1 ratio to either the treatment group or to the chemotherapy group. The randomization schedule was stratified by clinical site, and by patients who did or did not undergo re-operation for their recurrence to avoid unequal distribution of operated patients between study groups.

Follow Up: During treatment, and until progression for patients who stopped treatment before progression, all patients were seen once a month at an outpatient clinic where they underwent medical follow up and routine laboratory exams. Patients received a MRI every 2 months until disease progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months following disease progression. Patient survival was assessed monthly based on telephone interviews with the patients' caregivers.

Patient Characteristics: 237 patients (120 NovoTTF-100A; 117 chemotherapy) with progressive or recurrent GBM were enrolled in the study. Baseline characteristics were similar between treatment groups with slightly more men in the NovoTTF-100A group than in the chemotherapy group, and a lower incidence of frontal lobe tumors in the

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Study Population

Patients with previously diagnosed GBM who had relapsed or progressed despite conventional therapy (surgery and chemo-radiotherapy followed by chemotherapy) were recruited into the study. A total of 237 patients were enrolled in the study from 28 clinical centers. (US-16; Europe-11; and Israel-1) (See Appendix C for trial sites.). This number of patients is approximately 3% of the entire US population of recurrent GBM patients. The maximum number of patients recruited at one site was 21 patients, less than 10% of the total number of patients in the study. Approximately 50% of the patients were enrolled at the US sites. The final study analysis compared 120 NovoTTF-100A patients with 117 chemotherapy patients.

NOTE: the large study size and use of a control group compare favorably to the trial for bevacizumab in recurrent GBM, which had only 167 patients and no control arm. (Avastin Package Insert). Also note, the EF-11 trial of the NovoTTF-100A System is largest randomized clinical trial ever completed in this disease indication.

Key eligibility criteria follow:

• Inclusion Criteria

- Pathological evidence of GBM using WHO classification criteria
- ≥ 18 years of age
- Not a candidate for further radiotherapy or additional resection of residual tumor
- Subjects with disease progression (by Macdonald criteria (i.e., $> 25\%$ or new lesion)) documented by CT or MRI within 4 weeks prior to enrollment
- Karnofsky scale ≥ 70
- Life expectancy at least 3 months
- Participants of childbearing age must use effective contraception
- All subjects must sign written informed consent

• Exclusion Criteria

- Actively participating in another clinical treatment trial
- Within 4 weeks from surgery for recurrence
- Within 4 weeks from any prior chemotherapy
- Within 4 weeks from radiation therapy
- Pregnant
- Significant co-morbidities within 4 weeks prior to enrollment:
 - Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
 - Total bilirubin $>$ upper limit of normal
 - Significant renal impairment (serum creatinine > 1.7 mg/dL)
 - Coagulopathy (as evidenced by PT or APTT > 1.5 times control in subjects not undergoing anticoagulation)

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- Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
- Neutropenia (absolute neutrophil count $< 1 \times 10^3/\mu\text{L}$)
- Anemia (Hb $< 10 \text{ g/L}$)
- Severe acute infection
- Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias.
- Infra-tentorial tumor
- Evidence of increased intracranial pressure (midline shift $> 5\text{mm}$, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

Study Procedures

Treatment Arm: At treatment initiation, baseline examinations were performed and the investigator initiated NovoTTF-100A treatment under continuous medical supervision. The investigator also instructed patients on the operation of the NovoTTF-100A System and battery replacement. The patients then received continuous NovoTTF-100A treatment at home. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm: All patients had baseline examinations performed prior to treatment initiation. Patients received chemotherapy practiced at each of the participating centers. The effective chemotherapy treatments used in the study comprised mainly of the following chemotherapies: Bevacizumab (Avastin), platinum based chemotherapy (carboplatin), Nitrosureas (BCNU), procarbazine, lomustine and vincristine (PCV), temozolomide, and imatinib, erlotinib, irinotecan (mainly in Europe).

Randomization and Blinding: Patients who met the eligibility criteria were randomized in a 1:1 ratio to either the treatment group or to the chemotherapy group. The randomization schedule was stratified by clinical site, and by patients who did or did not undergo re-operation for their recurrence to avoid unequal distribution of operated patients between study groups.

Follow Up: During treatment, and until progression for patients who stopped treatment before progression, all patients were seen once a month at an outpatient clinic where they underwent medical follow up and routine laboratory exams. Patients received a MRI every 2 months until disease progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up continued for 2 months following disease progression. Patient survival was assessed monthly based on telephone interviews with the patients' caregivers.

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NovoTTF-100A group than in the chemotherapy group. Adjusted analyses for all pre-specified or all statistically significant baseline covariates for OS did not change the outcome of the trial. (See Table 2 below.) Four patients in the NovoTTF-100A group and 26 patients in the chemotherapy group never received any treatment on trial. (See Appendix D for patient disposition for all randomized patients.)

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Table 2. Demographics and Baseline Characteristics by Treatment Group

Statistically significant p-values (p<0.05) given in bold.

	NovoTTF-100A	CHEMOTHERAPY	
Characteristic	(N=120)	(N=117)	P-Value
Race			
Caucasian	111 (93)	106 (91)	Ns
African American	2 (2)	5 (4)	
Asian	0	3 (3)	
Hispanic	7 (6)	2 (2)	
Other	0	1 (1)	
Female Gender	28 (23)	44 (38)	0.0169
Frontal Tumor Position	38 (32)	58 (50)	0.0016
Bilateral or Midline Tumor Location	23 (19)	17 (15)	Ns
Prior Avastin Use	24 (20)	21 (18)	Ns
Re-operation for Recurrence	33 (28)	29 (25)	Ns
Prior Low-grade Glioma	12 (10)	11 (9)	Ns
Median Age (years) (min, max)	54 (24, 80)	54 (29,74)	Ns
Median Weight (kg)	80	80.5	Ns
Mean # of Prior GBM Recurrences	1.6	1.3	Ns
Mean KPS Score (min, max)	83±10.84	80.1±11.01	0.0456
Median Tumor Area (mm ²)	1440	1391	Ns
Median Time from GBM Diagnosis to Randomization (days)	334.5	340	Ns
Mean Time from last RT dose to Randomization (months)	13.71	13.93	Ns

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Effectiveness Results

Primary Effectiveness Endpoint: Overall Survival (OS)

In the pivotal trial, patients assigned to the NovoTTF-100A group had a median OS identical to those assigned to the effective chemotherapy group. In the ITT population, which included all randomized patients (Novo-TTF=120, chemo = 117), the median OS for NovoTTF patients was 6.3 months vs. 6.4 months for chemotherapy patients; $p=0.98$; $HR=1.0$. (See Table 3 below.) In the US, the median OS was 6.1 vs. 5.3 months in the ITT population. (See Table 4 below.)

- The pivotal study data establish that NovoTTF-100A therapy is comparable to chemotherapy in extending OS; 6.3 months vs 6.4 months.

Table 3. Primary Effectiveness Endpoint Analysis

	Novo TTF-100A (n=120)	Chemo (n=117)
Summary of Censored and Uncensored Value		
Number of Patients	120	117
Descriptive Statistics for OS (Months)		
Median (95% CI)	6.3 (5.6, 7.8)	6.4 (5.2, 7.4)
Minimum, Maximum	0.77, 42.03	0.03, 36.67

Table 4. Overall Survival by Region

	NovoTTF-100A [N=120]		Chemotherapy [N=117]	
COUNTRY	N	Median OS* (95% CI)	N	Median OS* (95% CI)
US	57	6.1 (4.0, 7.7)	58	5.3 (3.6, 7.2)
OUS	63	7.1 (5.6, 8.6)	61	7.2 (5.4, 8.5)

*Months United States (US), Outside United States (OUS)

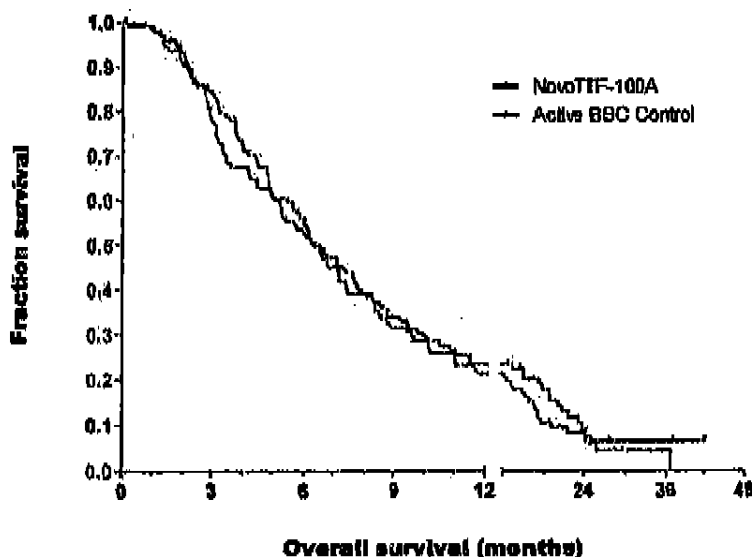
The Kaplan-Meier survival curve for the two treatment groups overlapped during the first 12 months of follow-up, where 80% of the events occurred in both groups. Between 12

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and 24 months, the survival curves separated slightly in favor of the chemotherapy control group. However, after 12 months, the number of patients remaining may be too small to reliably estimate the long term survival outcome. (See Figure 3 below.)

Figure 3. Kaplan-Meier Curves for Overall Survival



Secondary Effectiveness Endpoints: The one-year survival is the same in the NovoTTF-100A and chemotherapy groups, 21.9% vs. 22.1%. PFS6 was 21.4% NovoTTF-100A vs 15.2% chemotherapy and median TTP was 9.3 weeks for NovoTTF-100A vs. 9.6 weeks for chemotherapy. Radiological response rates were reported as 14% for the NovoTTF-100A group compared to 9.6% for the chemotherapy group. (See Table 5 below.)

- The secondary effectiveness endpoint results support the findings of the primary endpoint; they show the NovoTTF-100A device is clinically comparable to chemotherapy.

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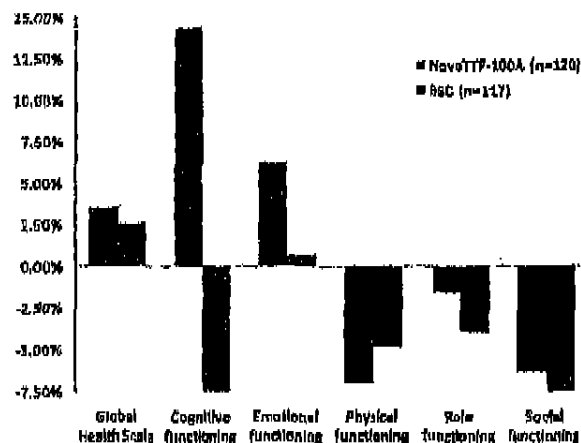
Table 6. Summary of Secondary Effectiveness Endpoints

Secondary Endpoints	Treatment Group	
	NovoTTF [®]	Chemo
N	120	117
1-year survival	21.9%	22.1%
PFSS	21.4%	15.2%
Radiological Response Rate (%)	14.0%	9.6%
Median TTP (weeks)	9.3	9.6

Quality of Life: QOL, based on validated questionnaires, was consistently higher for patients using the NovoTTF-100A than for patients receiving chemotherapy. Improvements were seen in five out of six general scales and seven out of nine symptom scales including, nausea, vomiting, diarrhea, constipation and pain. Additionally, major improvements were seen in emotional and cognitive functioning for the NovoTTF-100A patients. (See Figures 4 and 5 below.)

- QOL for patients treated with the NovoTTF-100A is significantly improved compared to patients treated with active chemotherapies.

Figure 4. Quality of Life-QLQ C30 General Scales

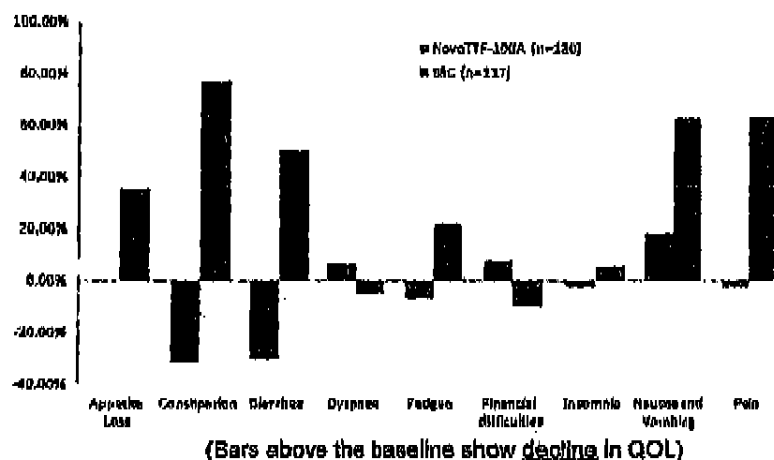


(Bars above the baseline show improvement in QOL)

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Figure 5. Quality of Life-QLQ C30 Symptom Scale



Safety Results: The NovoTTF-100A System was well tolerated by patients during the study as indicated by an average daily use of over 20 hours. The chemotherapy control patients experienced significantly more characteristic chemotherapy side effects than the NovoTTF-100A patients: gastrointestinal (30% vs. 8%), hematological (19% vs. 4%) and infections (12% vs. 4%). Mild to moderate skin reaction on the scalp beneath the device transducer arrays was observed in 16% of NovoTTF-100A patients. The investigators determined that none of these cases was severe. All resolved after discontinuing treatment, and all could be treated successfully with topical steroids and periodic shifting of transducer array positions. There was a lower incidence of AEs in almost all body systems in NovoTTF-100A. (See Figure 6 below.)

A similar incidence of serious adverse events (SAEs) was seen in both the NovoTTF-100A and CHEMOTHERAPY chemotherapy groups (13% vs. 11%, respectively). None of the SAEs was seen in more than 3% of patients. Three SAEs of convulsion and two SAEs of headache were reported in the NovoTTF-100A group. All five of these central nervous system (CNS) events in the NovoTTF-100A group were directly related to disease progression. (See Appendix E for complete list of AEs and SAEs.)

- The NovoTTF-100A is safe and well tolerated with significantly less toxicity than existing treatment options for recurrent GBM.

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Table 6. Treatment Emergent AEs by Body System

	Novo TTF-100A (n=118)	Chemotherapy (n=91)	p-value Chi-Squared
System Organ Class			
Blood and lymphatic system disorders	8 (4.3%)	17 (18.7%)	0.0009
Cardiac disorders	8 (6.8%)	8 (8.8%)	0.9313
Ear and labyrinth disorders	1 (0.8%)	3 (3.3%)	0.2066
Endocrine disorders	2 (1.7%)	2 (2.2%)	0.8059
Eye disorders	3 (2.6%)	5 (5.5%)	0.2813
Gastrointestinal disorders	9 (7.6%)	27 (29.7%)	<.0001
General disorders and administration site disorders	15 (12.6%)	14 (15.4%)	0.8137
Infections	5 (4.3%)	11 (12.1%)	0.0376
Injury, poisoning and procedural complications	21 (18.1%)	1 (1.1%)	<.0001
Investigations	8 (6.8%)	5 (5.5%)	0.6768
Metabolism and nutrition disorders	9 (7.6%)	12 (13.2%)	0.1992
Musculoskeletal and connective tissue disorders	6 (5.2%)	8 (8.8%)	0.3034
Neoplasms benign, malignant and unspecified (cysts and polyps)	2 (1.7%)	2 (2.2%)	0.8059
Nervous system disorders	50 (43.1%)	33 (36.3%)	0.319
Psychiatric disorders	12 (10.3%)	7 (7.7%)	0.5118
Renal and urinary disorders	7 (6.0%)	3 (3.3%)	0.3619
Respiratory, thoracic and mediastinal disorders	7 (6.0%)	10 (11.0%)	0.1975
Skin and subcutaneous tissue disorders	9 (7.6%)	9 (9.9%)	0.5691
Vascular disorders	5 (4.3%)	8 (8.8%)	0.4673

CONCLUSION: The pivotal study data established that the NovoTTF-100A System produces clinically comparable outcomes to chemotherapy, including bevacizumab (Roche; Avastin) across both primary (OS) and secondary effectiveness end-points for recurrent glioblastoma patients. The device produces these efficacy outcomes with fewer side-effects, including a reduced hospitalization rate, and provides the patients with an improved quality of life.

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Appendix A
FDA Approval Letter

http://www.accessdata.fda.gov/ocdrh_docs/pdf10/p100034a.pdf

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Appendix B

Summary of Preclinical Studies

TTFields have been shown both *in vitro* and *in vivo* to effectively inhibit cancer cell replication during mitosis without systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to effectively inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed), due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase. (Kirson, 2004)

Specifically, TTFields have been shown to inhibit glioblastoma cells *in vitro* and *in vivo* at a frequency of 200 kHz and an intensity of 0.7 V/cm RMS. Based on realistic finite element mesh simulations and direct measurements of TTFields intensity in experimental animals, and in the human brain, Novocure has concluded that effective TTField intensities can be generated in the brains of large animals and humans. Extensive safety studies in healthy animals (mice, rats and rabbits) have shown that TTFields are not associated with significant systemic toxicities. Neither acute nor chronic systemic toxicities were seen when TTFields were applied to the torso or head at different frequencies (100-200 kHz), different intensities or for different periods of time.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for the NovoTTF-100A device was determined to be approximately 4 weeks to reach tumor stabilization. This finding was later validated in independent animal studies and human pilot clinical studies. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

In Vitro Studies

Novocure has shown that when properly tuned, TTFields stunt the growth of tumor cells. This inhibitory effect has been demonstrated in all proliferating cell types tested; whereas, non-proliferating cells and tissues were unaffected. Different cell types showed specific intensity and frequency dependences of TTField-induced inhibition.

- **Mechanism of Action Studies:** Studies assessing the mechanism of action of TTFields have confirmed two main processes that occur at the cellular level during exposure to TTFields: 1) arrest of proliferation, and 2) dividing cell destruction. These mechanisms of action have been studied and confirmed via Novocure's early preclinical testing involving finite element simulations and calculations, and demonstrate no significant elevation in temperature compared to control cultures/mice.

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In addition to the above early studies, Novocure conducted studies using timelapse microphotography, colorimetric determination, staining of sub-cellular constituents, and measurements of electric fields to demonstrate the specific effects of TTFields on proliferating cancer cells grown in tissue culture, and to elucidate the mechanism of action of these effects. Based on these studies, it was determined that:

- TTFields arrest cell proliferation and result in cell death;
 - the inhibitory effects of TTFields are not limited to a specific cell type;
 - cell recovery can be prevented either by applying the TTFields for longer duration, or by applying fields in two directions normal to each other, that are interleaved in time; and
 - the axis of division of the dividing cells in relation to the electric fields is important in effecting cell death.
- **Proof of Concept Studies:** Novocure performed *in vitro* studies to assess the relationship between dose and frequency response using tumor cells from four of the most common types of cancer: malignant melanoma, glioblastoma, breast carcinoma and non-small cell lung carcinoma. This testing demonstrated that the optimal frequency of the fields is 200 kHz for rat glioblastoma (F-98) and human glioma (U-87), and that effective inhibition of glioma culture growth can be achieved at low field intensities (0.7-1.4 V/cm).

Finally, preclinical research both *in vitro* and *in vivo* has shown that, upon cessation of TTFields treatment, tumor growth rate does not increase beyond that seen before treatment, so that no rebound effect is expected.

- **Treatment Duration Simulations:** Novocure assessed tumor growth kinetics to evaluate optimal treatment duration and timing. Using a multi-compartmental model to simulate the growth kinetics of a malignant tumor, Novocure tested the time to tumor growth stabilization and reversal when exposed to TTFields using the NovoTTF-100A device. Based on the model, the minimal treatment course duration for the NovoTTF-100A device was determined to be approximately 4 weeks to reach tumor stabilization. This finding was validated in independent animal studies.

In Vivo Studies

Novocure conducted a series of early experiments in mice, rats, rabbits, sheep and pigs to verify the data that was previously obtained in prior simulations of TTField distribution. These experiments demonstrate that effective TTField intensities on the order of 0.7V/cm can be obtained within tumors in the brains of various animal models.

- **Animal Effectiveness Studies:** Novocure has shown that TTFields can be applied effectively to tumors through transducer arrays placed on the surface

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of the body. Using a special type of electrically insulated transducer array, significant inhibition of the growth of both intradermal melanoma (B16F1) in mice and intracranial glioma (F-98) in rats was seen after less than one week of treatment. (Kliron, 2007) In addition, Novocure has studied the effect of TTFields on metastatic spread of solid tumors and investigated the development of an immune response following TTField treatment. (Kliron, 2009) Importantly, in the rabbit kidney model, TTField treatment could be extended for up to 5 weeks due to the large size of the animals being used. Analysis of the time-dependence of the effect of TTFields in tumor bearing rabbits showed that a minimum TTField treatment duration of 4 weeks is necessary in order to achieve complete arrest of macroscopic tumor growth. Thus, the extrapolated minimal treatment course duration in GBM subjects was set at 28 days.

- **Animal Safety Studies:** Extensive safety studies in healthy rabbits and rats exposed to TTFields for protracted periods of time have shown no treatment related side effects or pathologic damage to the brain. The reasons for the low toxicity of TTField treatment can be explained in light of the known passive electric properties of normal tissues within the body and the effects of electric fields applied via insulated transducer arrays. In both acute and chronic application of TTFields to healthy animals, no evidence of abnormal cardiac rhythms or pathologic neurological activity is seen. In addition, no treatment related toxicities were found in any of the animal safety trials performed, even when field intensities 3 times higher than the effective anti-tumoral dose were applied. Finally, these studies demonstrated that hematopoietic cell replication should not be affected even with application of TTField intensities that are 10 times higher than necessary to inhibit tumor growth.

Biocompatibility, Electromagnetic Compatibility (EMC) and Electrical Safety, Shelf-Life and Software

The NovoTTF-100A System has passed extensive hardware and software verification and validation. The system also passed testing of applicable electrical safety and electromagnetic compatibility (EMC) standards at a certified laboratory. The transducer arrays that contact the subject were shown to be biocompatible in dermal sensitization, cytotoxicity and delayed type hypersensitivity studies. The batteries used with the system were shown to meet their specifications after more than 100 recharge cycles. Finally, the transducer arrays passed shelf life and sterilization validation according to the applicable standards. All of this testing demonstrates that the NovoTTF-100A System operates per its specifications and in accordance with its intended use.

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Appendix C

Pivotal Trial Sites and Investigators

United States

Center	Investigator
Memorial Sloan Kettering, NY	Dr. Philip Gutin
University of Virginia, VA	Dr. David Schiff
University of Illinois Chicago, IL	Dr. Herbert Engelhard
Northwestern Hospital, IL	Dr. Jeffrey Raiser
Beth Israel Deaconess Medical Center, MA	Dr. Eric Wong
University of Pittsburgh Medical Center, PA	Dr. Frank Liebermann
Evanston Northwestern, IL	Dr. Nina Paleologus
Columbia University, NY	Dr. Jeffrey Bruce
JFK Medical Center, NJ	Dr. Josef Landolfi
Allegheny Medical Center, PA	Dr. Lara Kunschner
Cleveland Clinic Foundation, OH	Dr. Robert Weil
Medical College Wisconsin, WI	Dr. Mark Malkin
Boston University, MA	Dr. Lawrence Chin
Lahey Clinic, MA	Dr. Rees Cosgrove
Well Cornell Medical Center, NY	Dr. Susann Pannullo
University Hospitals, OH	Dr. Andrew Sloan

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Outside United States

Center	Investigator
CHUV Lausanne, CH	Dr. Roger Stupp
Zurich University, CH	Dr. Silvia Hofer
Brno University Hospital, CZ	Dr. Martin Smrjca
Na Homolce Hospital – Prague, CZ	Dr. Vladimír Dbalý
Innsbruck University, AU	Dr. Franz Payer
Augsburg Clinic, DE	Dr. Volkmar Heidecke
University Graz, AU	Dr. Franz Payer
Tel Aviv Medical Center, IL	Dr. Andrew Kanner
Hopital de la Pitié-Salpêtrière, FR	Dr. Sophie Tallibert
CHU Lyon, FR	Dr. Jerome Honnorat
University of Kiel, DE	Dr. Maximilian Mehdron
University of Hamburg, DE	Dr. Manfred Westphal

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Appendix D Adverse Events

Adverse Events by Body System (Incidence > 2%)

	TTF THERAPY [N=118]	CHEMOTHERAPY [N=81]
System Organ Class	# of Pts.	# of Pts.
Preferred Term	(Incidence)	(Incidence)
Number with ≥1 AE	64 (56)	54 (68)
Blood and lymphatic system disorders	6 (4)	17 (19)
Leukopenia	1 (1)	6 (7)
Lymphopenia	2 (2)	3 (3)
Thrombocytopenia	3 (3)	11 (12)
Cardiac disorders	8 (7)	6 (7)
Edema peripheral	6 (5)	3 (3)
Tachycardia	1 (1)	3 (3)
Ear and labyrinth disorders	1 (1)	3 (3)
Eye disorders	3 (3)	6 (6)
Gastrointestinal disorders	9 (8)	27 (30)
Abdominal pain	0 (0)	6 (7)
Constipation	2 (2)	4 (4)
Diarrhea	0 (0)	11 (12)
Nausea	3 (3)	15 (18)
Vomiting	3 (3)	6 (7)
General disorders and administration site conditions	16 (13)	14 (16)
Fatigue	11 (9)	10 (11)
Infections and infestations	8 (4)	11 (12)
Candidiasis	4 (3)	3 (3)
Urinary tract infection	0 (0)	3 (3)
Injury, poisoning and procedural complications	21 (18)	1 (1)
Fall	5 (4)	0 (0)
Medical device site reaction	18 (16)	0 (0)
Investigations	5 (7)	5 (5)
Metabolism and nutrition disorders	9 (8)	12 (13)
Anorexia	0 (0)	4 (4)
Hyperglycemia	2 (2)	2 (2)
Hypokalemia	2 (2)	1 (1)

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	TTF THERAPY (N=116)	CHEMOTHERAPY (N=91)
System Organ Class	# of Pts.	# of Pts.
Preferred Term	(Incidence)	(Incidence)
Musculoskeletal and connective tissue disorders	6 (5)	8 (9)
Back pain	2 (2)	3 (3)
Muscular weakness	0 (0)	3 (3)
Pain in extremity	0 (0)	2 (2)
Nervous system disorders	60 (43)	33 (30)
Amnesia	3 (3)	0 (0)
Convulsion	11 (9)	4 (4)
Coordination abnormal	2 (2)	4 (4)
Cranial nerve disorder	3 (3)	1 (1)
Dizziness	3 (3)	2 (2)
Dysphasia	4 (3)	2 (2)
Headache	18 (16)	9 (10)
Hemianopia	2 (2)	4 (4)
Hemiparesis	11 (9)	4 (4)
Hyperreflexia	3 (3)	2 (2)
Hypoesthesia	2 (2)	3 (3)
Nervous system disorder	3 (3)	3 (3)
Psychiatric disorders	12 (10)	7 (6)
Depression	2 (2)	5 (5)
Mental status changes	8 (6)	1 (1)
Renal and urinary disorders	7 (6)	6 (3)
Urinary incontinence	4 (3)	2 (2)
Respiratory, thoracic and mediastinal disorders	7 (6)	10 (11)
Cough	4 (3)	4 (4)
Dyspnea	2 (2)	4 (4)
Skin and subcutaneous tissue disorders	9 (8)	9 (10)
Alopecia	0 (0)	3 (3)
Rash	6 (4)	0 (0)
Vascular disorders	5 (4)	8 (7)
Hypertension	1 (1)	3 (3)

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Serious Adverse Events by Body System

	NovoTTF-100A [N=116]	CHEMOTHERAPY [N=91]
	# of Pts.	# of Pts.
Preferred Term	(Incidence)	(Incidence)
Number with ≥1 SAE	15 (13)	10 (11)
Febrile neutropenia	0 (0)	1 (1)
Peripheral edema	2 (2)	0 (0)
Intestinal perforation	0 (0)	1 (1)
General physical health deterioration	1 (1)	0 (0)
Cellulitis	0 (0)	1 (1)
Pneumonia	0 (0)	1 (1)
Urinary tract infection	0 (0)	1 (1)
Cerebrospinal fluid leakage	1 (1)	0 (0)
Anorexia	0 (0)	1 (1)
Dehydration	1 (1)	0 (0)
Neoplasm progression	2 (2)	2 (2)
Convulsion	3 (3)	0 (0)
Headache	2 (2)	0 (0)
Nervous system disorder	0 (0)	1 (1)
Mental status changes	1 (1)	0 (0)
Dyspnea	1 (1)	0 (0)
Cerebral hemorrhage	1 (1)	0 (0)
Pulmonary embolism	1 (1)	2 (2)

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NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality

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^a University of Innsbruck, Austria^b University Hospital Zurich, Switzerland^c Columbia University Medical Center, New York, NY, United States^d Lahey Clinic, Boston, MA, United States^e NorthShore University Health System, Evanston, IL, United States^f Memorial Sloan Kettering Cancer Center, New York, NY, United States**KEYWORDS**

Glioblastoma

Brain tumour

Chemotherapy

Randomised trial

Abstract *Purpose:* NovoTTF-100A is a portable device delivering low-intensity, intermediate frequency electric fields via non-invasive, transducer arrays. Tumour Treatment Fields (TTF), a completely new therapeutic modality in cancer treatment, physically interfere with cell division.

Methods: Phase III trial of chemotherapy-free treatment of NovoTTF (20–24 h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. Primary endpoint was improvement of overall survival.

Results: Patients (median age 54 years (range 23–80), Karnofsky performance status 80% (range 50–100) were randomised to TTF alone ($n = 120$) or active chemotherapy control ($n = 117$). Number of prior treatments was two (range 1–6). Median survival was 5.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66–1.12]; $p = 0.27$), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% ($p = 0.13$), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, $p = 0.19$). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% ($p = 0.022$) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favoured TTF therapy in most domains.

Conclusions: This is the first controlled trial evaluating an entirely novel cancer treatment modality delivering electric fields rather than chemotherapy. No improvement in overall survival was demonstrated, however efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma. Toxicity and quality of life clearly favoured TTF.

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1. Background

Glioblastoma is the most prevalent primary malignant brain tumour in adults. Median survival with optimal therapy is only 15 months from diagnosis, and most tumours recur within 9 months of initial treatment.¹ At the time of disease recurrence, treatment options for glioblastoma patients are limited. Repeat surgery may be considered in approximately 20% of patients,^{2–4} and re-irradiation is possible in rare circumstances. For most patients chemotherapy is indicated at disease recurrence, with the choice of drug varying greatly. In the United States, bevacizumab has been provisionally approved for recurrent glioblastoma, while the European Medicines Agency (EMA) rejected the application in the absence of a controlled trial.^{5,6} Cytotoxic agents most frequently used are alkylating agents like nitrosoureas (e.g. lomustine [CCNU] or carmustine [BCNU]),⁷ procarbazine⁸ or re-treatment with temozolomide.^{9,10} Response rates are below 10%, progression-free survival rates at 6 months <20%.^{7,8} In the absence of an established and satisfactory standard treatment, bevacizumab

alone and in combination with irinotecan and experimental treatments are commonly used.^{11–13}

Overall survival (OS) from recurrence is commonly short and without effective therapy rarely exceeds 3–5 months.^{14–19} In a randomised trial of repeat surgery with implantation of carmustine wafers versus placebo median survival was 5.5 versus 4.7 months.²⁰ With active therapy, a median survival of 7 months (range 5–9.2 months)^{7–10,12,13,21–24} has been reported. A recent randomised comparison of enzastaurin versus lomustine at first recurrence demonstrated a median survival of 7.1 months, with 19% of patients alive and progression-free at 6 months when treated with lomustine.⁷ Based on these results active chemotherapy as salvage treatment for patients with recurrent glioma is recommended, which strives to improve survival and quality of life despite inherent chemotherapy-related toxicity.

The NovoTTF-100A system (Novocure Ltd., Haifa, Israel) is a portable device delivering low intensity, intermediate frequency, alternating electric fields (Tumour Treating Fields; TTF) using non-invasive, disposable transducer arrays (Fig. 1A). These fields physically

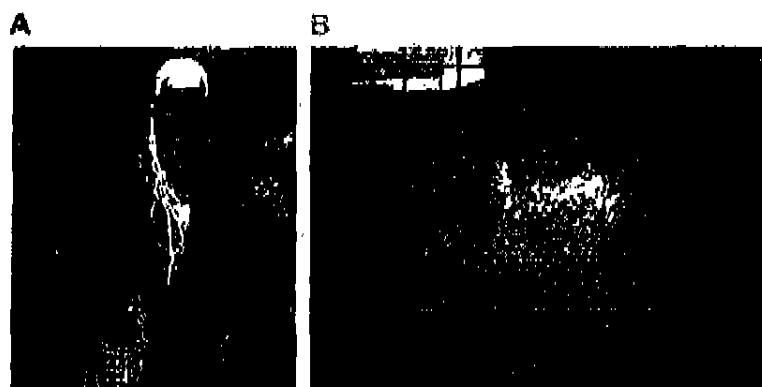


Fig. 1. Female patient wearing the portable NovoTTF-100A device (A). Grade 2 skin rash underneath transducer arrays in a different patient (B). With the patients' permission.

interfere with cell division by causing misalignment of microtubule subunits in the mitotic spindle during the metaphase to anaphase transition²⁵ and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase.^{26,27} This causes failure of cytokinetic furrow formation and resultant mitotic blebbing, leading to the disruption of chromosome segregation and eventual cell death. The exact pathways by which spindle disruption and physical aggregation of macromolecules lead to cell death are unknown. TTF has been tested in several pilot clinical studies^{26,28,29} including a small single arm study as monotherapy for recurrent glioblastoma. The results of this pilot trial were promising²⁶ and served as the basis of this phase III trial comparing NovoTTF-100A monotherapy (TTF) to best active chemotherapy according to the physician's best choice (active treatment control group). This report describes for the first time the efficacy and safety of this entirely novel treatment modality compared to widely accepted active chemotherapies for the treatment of recurrent glioblastoma patients.

2. Methods

2.1. Patient selection

Patients 18 years or older with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) were eligible following radiologically confirmed disease progression (Macdonald criteria). Patients had a Karnofsky performance status $\geq 70\%$ and adequate haematologic, renal and hepatic function (absolute neutrophil count $\geq 1000/\text{mm}^3$; haemoglobin $\geq 100 \text{ g/L}$ platelet count, $\geq 100,000/\text{mm}^3$; serum creatinine level $\leq 1.7 \text{ mg/dL}$ ($<150 \mu\text{mol/L}$); total serum bilirubin level \leq the upper limit of normal and liver-function values, <3 times the upper limit of normal). Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temozolomide). There was no limit on number or type of prior

therapies or recurrences. Patients with infra-tentorial tumour location were excluded, as were patients with implanted electronic medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt). All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centres.

2.2. Study design and treatment

Patients were randomised at a 1:1 ratio to receive either TTF monotherapy (without chemotherapy) or the best available active chemotherapy according to the local physician's choice (active control). Randomisation was performed using random block sizes and was stratified by centre and according to whether patients underwent surgery for their latest recurrence prior to trial entry. Assigned treatment had to start within 1 week of randomisation, and was to be continued until disease progression or intolerance.

For patients assigned to the TTF group four transducer arrays were placed on the patient's shaved scalp and connected to a portable, battery or power supply operated device (NovoTTF-100A) which was set to generate 200 kHz electric fields within the brain in two perpendicular directions (operated sequentially). Field intensity was set at $>0.7 \text{ V/cm}$ at the centre of the brain. Patients were trained on how to operate the device and then continued treatment at home. Treatment was continuous while maintaining normal daily activity. Transducer arrays were replaced by the patients, their caregivers or device technicians once or twice a week. Prior to placement, the scalp was shaved carefully with an electric razor in order to avoid skin wounding, transducer arrays were supplied sterile. Although uninterrupted treatment was recommended, patients were allowed to take treatment breaks of up to an hour, twice per day, for personal needs (e.g. shower). In addition, they were allowed to take 2–3 days off treatment at the end of each 4 weeks of treatment (which is the minimal

required treatment duration for TTF therapy to reverse tumour growth).³⁰

Patients assigned to the active control received chemotherapy at the local investigators discretion. The best available chemotherapy was prescribed according to local practice and depending on prior treatment exposure.

2.3. Patient surveillance and follow up

Baseline examinations included a gadolinium-enhanced magnetic resonance imaging (MRI) of the brain, full blood counts, blood chemistry tests, blood coagulation tests, electrocardiogram (ECG), physical examination including a detailed neurological examination and quality of life (QoL) questionnaire (European Organisation for Research and Treatment of Cancer (EORTC) QLQ C-30).

Patients were followed once a month, including laboratory tests. MRI was repeated every 2 months. QoL questionnaires were completed at baseline and then every 3 months. Tumour response and progression were determined by blinded central radiology review, according to Macdonald criteria.³¹ When an MRI could not be obtained, progression was assessed clinically based on neurological status, steroid dosing, adverse events and investigator assessment of progression.

Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria (NCI CTC V3.0)

2.4. Statistical analysis

The primary end-point was OS. Secondary end-points were progression free survival (PFS), the percentage of patients alive and progression-free at 6 months (PFS6), 1-year survival rate, radiological response rate (RR), QoL and safety. OS and PFS were computed from the day of randomisation until event or censored at last follow-up according to the Kaplan-Meier method, with 2-sided logrank statistics for comparison. The study had an 80 per cent power at a significance level of 0.05 to detect a 60 per cent increase in median OS (hazard ratio for death, 0.63). All analyses were performed using the intent to treat population of all randomised patients, patients lost to follow-up were censored at the time of last contact. A Cox proportional hazards model was used to adjust for confounding baseline variables (continuous and categorical). The survival data were tested for proportional hazards and the assumption of proportionality met. The Cox model was performed in two steps; first, all protocol pre-specified baseline variables were tested directly for interactions with OS; then a reduced model was performed testing the effect of all variables with significant interactions ($p < 0.05$) with OS together on the treatment effect of TTF versus active chemotherapy. Secondary end-points are presented without adjustment. QoL is pre-

sented as change from baseline to 3 months for each of the subscale domains and symptom scales of the QLQ-C30 questionnaire.

2.5. Organisational aspects

The trial was registered on www.clinicaltrials.gov, NCT#00379470. The trial was funded and sponsored by Novocure Ltd. Statistical analysis was performed by David Steinberg. The manuscript was written by Roger Stupp and Eilon Kirson, with substantial input by all co-authors. The final manuscript was reviewed and approved by all authors. The statistician and the corresponding author had unrestricted access to all data.

2.6. Role of the funding source

Representatives of the study sponsor were involved in the study design, data collection, data analysis, data interpretation and writing of the report. Data analysis was performed by David Steinberg, a compensated independent biostatistician. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Patients

From September 2006 until May 2009, 237 patients from 28 institutions in 7 countries were randomly assigned to receive TTF monotherapy (120 patients) or active control chemotherapy (117 patients). The baseline patient characteristics were balanced (Table 1). The median age was 54, and a quarter of the patients had undergone some surgical resection of the recurrent tumour prior to enrolment into the trial. More than 80% of patients had failed two or more prior lines of chemotherapy (\geq second recurrence) and 20% of the patients had failed bevacizumab prior to enrolment. Histology was per local pathological diagnosis; in 8% a history of a prior lower grade glioma had been reported (secondary glioblastoma). *Methyl-guanine methyl-transferase (MGMT)* gene promoter methylation, an important predictive factor for benefit of temozolomide chemotherapy in newly diagnosed glioblastoma, was not assessed in this trial of patients with recurrent disease.

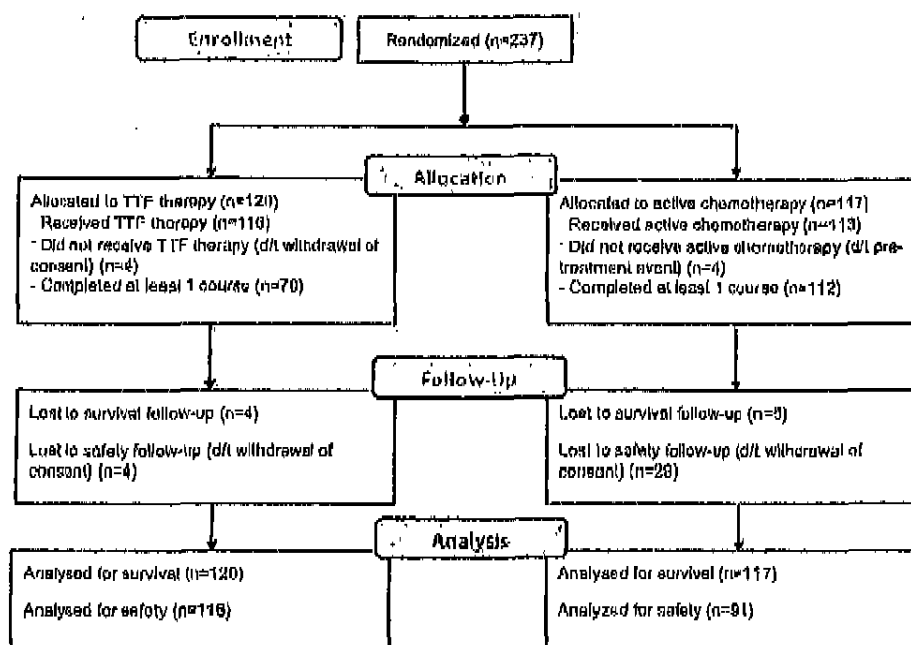
3.2. Patient disposition, treatment and compliance

In the TTF group, 116 of 120 patients (97%) started treatment and 93 patients (78%) completed 4 weeks of therapy (1 cycle). Twenty-seven patients discontinued treatment early, often within a few days, due to non-compliance or inability to handle the device (trial flow

diagram). Four patients had pre-treatment events related to the progressive nature of their disease and never started therapy with the device. In the TTF patients who started treatment (116 patients) mean compliance was measured by downloading a log file from the device, which recorded the actual time TTF therapy was delivered. Median compliance was 86 per cent (range 41–98%) of the time in each treatment month, translating into a mean use of 20.6 h per day.

apy (6.6 versus 6.0 months, respectively). One-year survival proportion was 20% in both groups, the 2- and 3-year survival rates survival rates were 8% (95% CI 4, 13) and 4% (95% CI 1, 8) versus 5% (95% CI 3, 10) and 1% (95% CI 0, 3), for TTF versus active control, respectively (Fig. 1A). The hazard ratio for death was 0.86 (95% CI 0.66, 1.12) in favour of NovoTTF ($p = 0.27$). Adjusting for baseline characteristics using a Cox proportional hazards model did not substantially

trial flow diagram



In the active control group, 113 of 117 patients (97%) started chemotherapy and all but 1 patient completed one full treatment course of the chosen chemotherapy. In four patients disease related adverse events and tumour progression prevented the initiation of the planned chemotherapy, they only received supportive care (hospice care). Twenty-one patients randomised to the control group decided not to return to the investigational site for treatment, thus details on disease progression and toxicity are not available. Most of patients received single agent or a combination chemotherapy regimen containing bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%; Supplementary Table 1).

3.3. Survival, progression and radiological response

At a median follow up of 39 months, 220 patients had died (93%). Median survival was marginally higher in the TTF group compared to active control chemother-

apy after the results. In the active chemotherapy control arm of the trial, survival was not significantly affected by the choice of chemotherapy (Cox proportional hazards test; $p = 0.66$).

More objective radiological responses (partial and complete responses) were seen in the TTF group than in the active control chemotherapy groups (14 versus 7, respectively), translating into a response rate in evaluated patients of 14.0% (95% CI 7.9–22.4%) versus 9.6% (95% CI 3.9–18.8%), respectively (chi squared $p = 0.19$). All three complete responses were observed in the TTF group. Two exemplary partial responses from TTF are shown in Fig. 3.

The trial had been designed for superiority. Since the control group in the trial is an active chemotherapy control which showed similar efficacy to that seen in previous trials and the device was used as monotherapy it is reasonable to analyse the results also in the context of a non-inferiority analysis. The HR for death in the TTF group compared to the active control chemotherapy group was below 1.0 (0.86; 95% CI 0.66–1.12), indi-

Table 1
Baseline characteristics.

	Tumour Treatment Fields (TTF) (n = 120) # pts (%)	Active control (n = 117) # pts (%)
Characteristics		
Age, median (range)	54 years (24–80)	54 years (29–74)
Gender		
Male	92 (77)	73 (62)
Female	28 (23)	44 (38)
Histology		
Glioblastoma	100%	100%
Prior lower grade glioma	10 (8)	9 (8)
Karnofsky performance status, median (range)	80% (50–100)	80% (50–100)
Steroid use at enrolment		
Yes	55 (46)	62 (53)
No	55 (46)	49 (42)
Unknown	10 (8)	6 (5)
Largest tumour diameter at randomisation, median (range)	6.1 cm (0–15.2)	5.5 cm (0–16.2)
Interval from initial glioma diagnosis, median (range)	11.8 months (3.2–99.3)	11.4 months (2.9–77.1)
Prior therapy		
1st recurrence	11 (9)	17 (15)
2nd recurrence	38 (48)	54 (46)
3rd or greater recurrence	51 (43)	46 (39)
Surgery		
Debulking before enrolment	33 (28)	29 (25)
Debulking at any stage	95 (79)	99 (85)
Biopsy only	25 (21)	18 (15)
Radiotherapy		
With concomitant temozolomide	100%	100%
No concomitant temozolomide	15 (13)	20 (17)
Unknown	2 (1)	1 (1)
Prior adjuvant (maintenance) temozolomide		
Median no of cycles	4 (0–19)	3 (0–27)
Prior bevacizumab		
	23 (19)	21 (18)

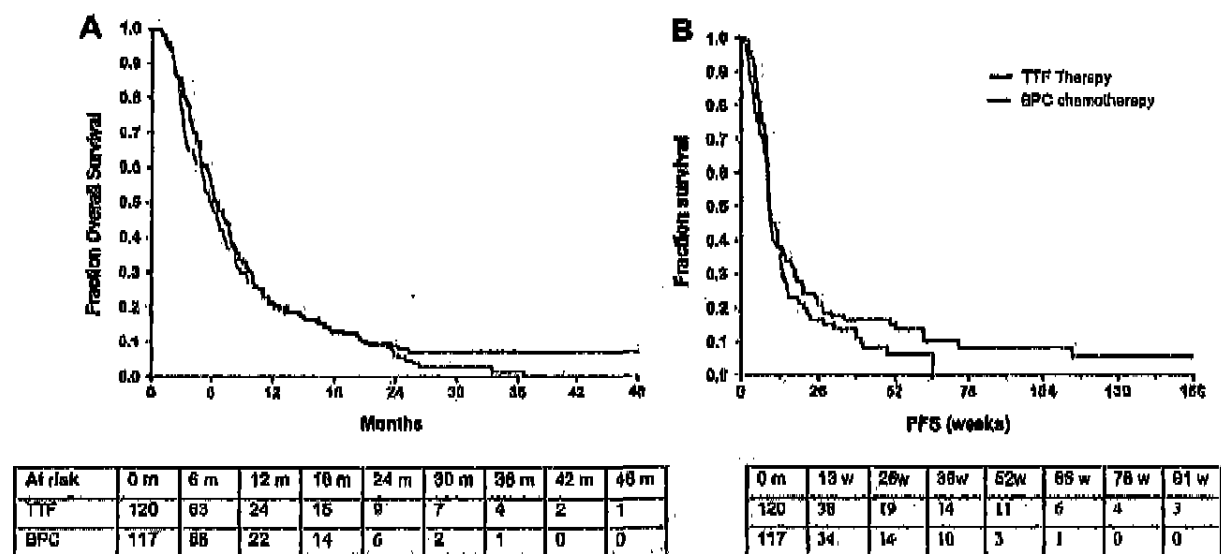


Fig. 2. Overall survival (A) and progression free survival (B) Kaplan-Meier curves.

cating that TTF may be at least equivalent to active chemotherapy.

PFS showed a similar trend in favour of TTF patients as seen for OS (Fig. 1B). Median PFS was 2.2 and

2.1 months for TTF and active control groups, respectively (Fig. 2; HR 0.81, 95% CI 0.60–1.09; log rank $p = 0.16$). PFS6 was 21.4 per cent (95% CI 13.5–29.3) in the TTF group and 15.1 per cent (95% CI 7.8–22.3) in the active control group (chi squared $p = 0.13$).

3.4. Safety and toxicity

As expected from the mechanism of action of TTF therapy and the fact that its delivery is localised to the head, the typical systemic side-effects of chemotherapies were not observed in the TTF treated patients. Mild to moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16% of TTF patients (Fig. 1B). This condition was easily treated with topical corticosteroids, resolved completely after treatment, was stopped and did not require substantial treatment breaks.

Patients receiving active control chemotherapy experienced toxicity related to pharmacologic mechanism of the agents used. A list of grade 2–4 adverse events by organ system and adverse event terms seen in more than 2% of patients in either group is presented in Table 2. As expected, there were significantly more gastrointestinal, haematological and infectious adverse events seen in the chemotherapy group than in the TTF group. Severe

(grades 3 and 4) toxicity was observed in only 3% of patients.

3.5. Quality of life

Longitudinal Quality of Life (QOL) could be analysed in the patients who remained on study therapy for ≥ 3 months and for whom QoL data were available (63 patients, 27%). In the domains of global health and social functioning no meaningful differences between chemotherapy and TTF were observed. However, cognitive and emotional functioning favoured TTF. Physical functioning may be slightly worse with TTF, while role functioning favoured TTF (Fig. 4A). Symptom scale analysis is in accordance to treatment-associated toxicity; appetite loss, diarrhoea, constipation, nausea and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF treatment group (Fig. 4B).

3.6. Treatment after progression

In order to rule out the effect of subsequent treatments on the OS results reported above, we compared the number and type of post-progression treatments patients received after failing the trial therapy. Due to

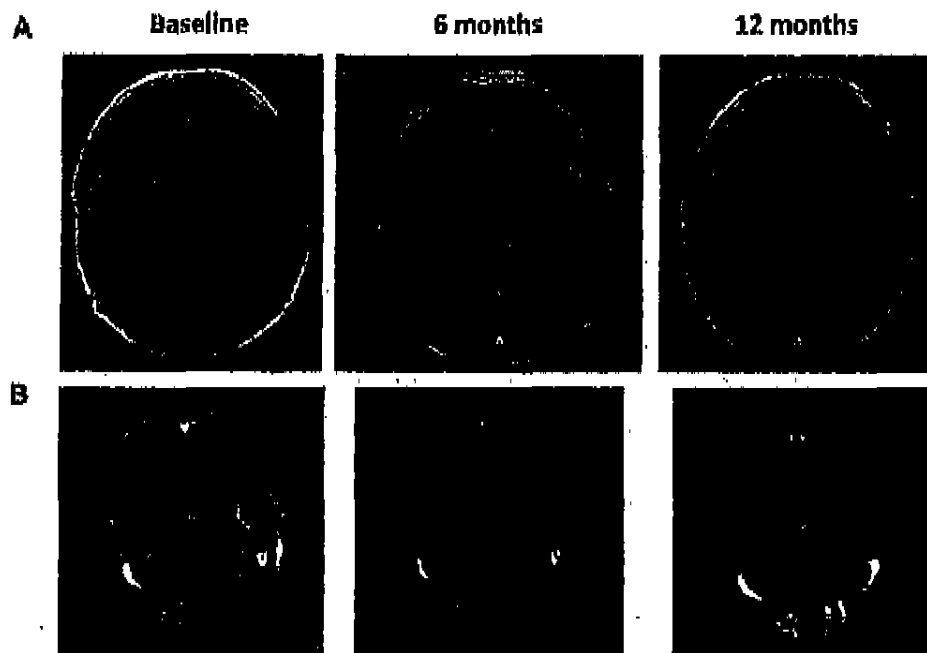


Fig. 3. Exemplary T1 weighted magnetic resonance imaging (MRI) images with gadolinium from two Tumour Treatment Fields (TTF) patients with partial response to therapy. (A) A 48 years old male with prior grade II astrocytoma which transformed to glioblastoma (based on tissue biopsy). The subject progressed 7 months after receiving chemoradiotherapy, and subsequently responded to TTF therapy (partial response at 12 months) and remained stable for an additional 36+ months on TTF. (B) A 55 years old male with primary glioblastoma who recurred for the third time after receiving chemoradiotherapy, adjuvant temozolomide (2 cycles), bevacizumab with irinotecan (3 months) and erlotinib with sorafenib (one cycle). The subject had a partial response to TTF therapy after 4 months of treatment and remained stable for an additional 8 months while on TTF.

Table 2
Treatment-emergent adverse events \geq grade 2 by body system.

System	Adverse event term	Tumour Treatment Fields (TTF) (n = 116) % (% gr. 3 + 4)	Active control (n = 91) % (% gr. 3 + 4)
Hematological		3 (0)	17 (4)
	Leucopenia	0 (0)	5 (1)
	Neutropenia	0 (0)	2 (1)
	Thrombocytopenia	1 (1) ^a	7 (2)
Gastrointestinal disorders		4 (1)	17 (3)
	Abdominal pain	0 (0)	3 (0)
	Diarrhoea	0 (0)	6 (2)
	Nausea/vomiting	2 (0)	7 (0)
General deterioration and malaise		5 (1)	6 (1)
Infections		4 (0)	8 (1)
Skin rash (transducer arrays)		2 (0)	0 (0)
Metabolism and nutrition disorders		4 (1)	6 (3)
Musculoskeletal disorders		2 (0)	5 (0)
Nervous system disorders		30 (7)	28 (7)
	Brain oedema	0 (0)	2 (0)
	Cognitive disorder	2 (1)	2 (1)
	Convulsion	7 (2)	5 (2)
	Dysphasia	2 (0)	1 (0)
	Headache	8 (1)	6 (0)
	Hemianopsia	1 (0)	3 (1)
	Hemiparesis	3 (1)	2 (1)
	Neuropathy peripheral	2 (0)	2 (0)
Psychiatric disorders		5 (0)	4 (0)
Renal and urinary disorders		3 (1)	3 (0)
Respiratory disorders		1 (0)	3 (1)
Vascular disorders		3 (1)	4 (3)
	Pulmonary embolism	1 (1)	2 (2)
	Hypertension	1 (0)	1 (1)
	Deep vein thrombosis	1 (0)	1 (0)

^a Thrombocytopenia from prior chemotherapy, normalised subsequently.

the very advanced stage they were recruited to the study (most patients were at their second or subsequent recurrence), only 5.8% of the TTF-treated patients and 10.3% of the chemotherapy-treated patients received subsequent salvage antitumour therapy (chi square $p = 0.24$) (mainly bevacizumab, irinotecan, nitrosoureas and temozolomide). The majority of patients received only supportive care once tumour progression developed.

4. Discussion

Tumour treatment with alternating electrical fields that interfere with the metaphase to anaphase transition in dividing tumour cells is an entirely novel cancer treatment modality. We report the first prospective, randomised, controlled study using this new treatment modality in the most aggressive primary brain tumour. Although glioblastoma diffusely infiltrates the brain, it almost never metastasises and is thus amenable to a loco-regional therapy.

Prognosis of patients with recurrent glioblastoma is poor, and chemotherapy is usually recommended. Depending on prior treatments and treatment centre expertise, variable chemotherapy agents alone or in combination are commonly prescribed. Our randomised trial compared this standard chemotherapy per local

practice (active treatment control group) with TTF in a prospective, multicentre phase III trial. Although the trial did not reach its primary end-point of improved survival compared to active chemotherapy, this new minimally invasive and chemotherapy-free local treatment modality demonstrated a statistically non-significant increased response rate (14 versus 9.5%, $p = 0.19$), an improved PFS6 rate (21% versus 15%, $p = 0.13$), and a trend towards reduction of the risk of death (hazard ratio 0.86, 95% CI 0.66–1.12, $p = 0.27$), as well as sustained improvement in QoL.

These results cannot be explained by subsequent salvage chemotherapy, as few patients received additional therapy after failure of protocol treatment. Importantly, the majority of our patients were recruited to the trial at an advanced stage of the disease, after failure of two or more chemotherapy agents, while other trials in recurrent glioblastoma usually only enrol patients at first recurrence. It is also notable that 20% of patients had failed prior bevacizumab therapy, a population that usually fares poorly with most subsequent treatments.

One limitation of the study was the absence of a placebo or treatment-free control arm. In the setting of advanced disease and chemotherapy considered indicated and effective, such a control would hardly have been acceptable to patients and physicians alike. Fur-

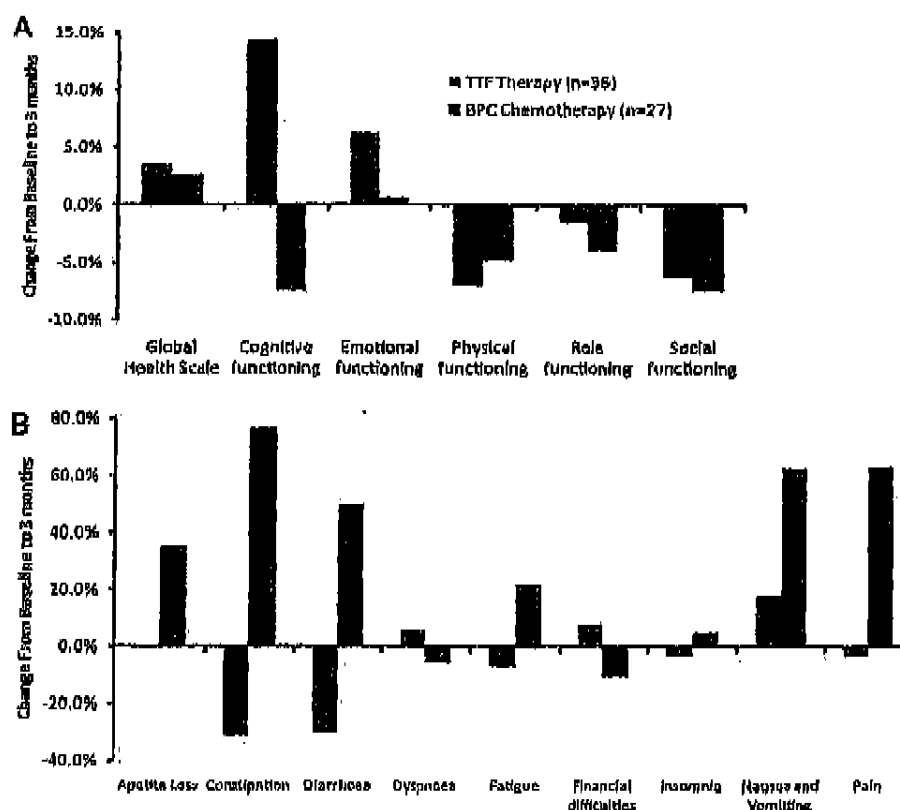


Fig. 4. QLQ C30 longitudinal change from base to 3 months. (A) General functional scales (an increase in percentage corresponds to an increase in QOL). (B) Symptom scales (an increase in percentage corresponds to a decrease in QOL).

thermore, chemotherapy with lomustine has shown superior efficacy versus investigational treatments in two recent randomised trials. And based on high response rates and prolonged survival compared to historical controls bevacizumab has received accelerated Food and Drug Administration (FDA) approval. Furthermore, the observation of objective responses in 14 patients with NovoTTF alone (median time since end of prior RT 7 months, thus unlikely to be all pseudoprogression) strongly suggests singular activity of this device.

Another limitation is the somewhat heterogeneous patient population, with patients included after progression of one or several lines of prior chemotherapy. This underscores the demand from patients for further treatments, even when the expected benefit of a 2 months prolongation in PFS may appear modest. In the ongoing randomised phase III trial for newly diagnosed glioblastoma, only patients non-progressive after completion of chemoradiation are eligible (Novocare EF-14, www.clinicaltrials.gov, NCT#00916409).

As expected with a local treatment, toxicity was limited to skin irritation from transducer arrays (Fig. 1B). After proper instructions, most patients became independent in handling this device and replacing transducer arrays, allowing them to be ambulatory and even going to work. Despite the inconvenience of carrying and

using the device almost permanently, compliance was high and patients reported improvement in QoL in the absence of chemotherapy related toxicities.

In vitro and animal experiments suggest enhanced effect when TTF is combined with chemotherapy.^{20,32} We therefore initiated a subsequent randomised phase III trial currently enrolling newly diagnosed glioblastoma patients after completion of standard radio-chemotherapy, parallel to starting the adjuvant or maintenance temozolomide chemotherapy. Patients randomised to the experimental arm will receive TTF in addition to maintenance temozolomide (www.clinicaltrials.gov, NCT#00916409).

Based on the result of this trial TTF therapy has recently been approved in the US and Europe for the treatment of recurrent glioblastoma (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251669.htm).

The universal anti-cancer effect of TTF may be applicable to other solid tumour types, alone or in combination with chemotherapy. In particular, in a situation of morbidity induced by a heavy local tumour burden, and in conditions where further radiotherapy is not an option, this non-invasive treatment may allow for a clinical benefit and will substantially expand our treatment armamentarium.

Conflict of interest statement

Eilon Khron and Uri Weinberg are employees of Novocure Ltd., and have stock options in the company.

Herwig Kostron has received honoraria from Novocure Ltd.

Yoram Palti is the inventor of the Novo-TTF principle. He received consulting honoraria and travel support by Novocure Ltd.

Nina Paleologos has served on advisory boards and speakers bureau to Genentech, Merck & Co (previously Schering-Plough).

Susan Panullo has received research grants from Novocure, NTI Pharma, Eisai, Immunocellular and Parexel, and honoraria for lectures from Merck & Co (previously Schering-Plough).

Zvi Ram is a board member for Novocure, and received consultancy honoraria.

Jeffrey Raizer has received research support from Novocure Ltd., performed consultancy for Merck and Genentech/Roche, and lectures on behalf of Merck & Co, Genentech and Enzon.

David Schiff has performed consultancy for Genentech and Tan Pharmaceuticals.

Andrew Sloan has provided consultancy to Genentech/Roche, Real Bio Inc., Nanfiber Solutions, Surgical Theatre and Monteris Medical Inc.

Roger Stupp has served on scientific advisory boards for Merck-Serono, Roche, Actelion, MDxHealth (previously OncoMethylomeSciences) and Merck and Co (previously Schering-Plough).

Manfred Westphal has received consultancy honoraria from Roche, OncoScience and Ark Therapeutics.

Eric T. Wong has received research support from Novocure Ltd.

The following authors declare no potential conflict of interest: Jeffrey Bruce, Lawrence Chin, Rees Cosgrove, Vladimir Dbaly, Herbert Engelhard, Philip Gutin, Volkmar Heidecke, Silvia Hofer, Andrew Kanner, Lara Kunscher, Joseph Landolfi, Frank Lieberman, Marc Malkin, Maximilian Mehdorn, Franz Payer, Martin Stroka, David Steinberg, J. Lee Villano, and Robert Weil.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejca.2012.04.011>.

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EXPERT REVIEWS

NovoTTF-100A: a new treatment modality for recurrent glioblastoma

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NovoTTF-100A (Novocure Inc., Haifa, Israel) is a first-of-a-kind device approved by the US FDA for the treatment of recurrent glioblastoma. It works by emitting a low-intensity, intermediate-frequency (200 kHz), alternating electric field administered via insulated transducer arrays applied onto the scalp. The electric field penetrates the brain and inhibits the growth and proliferation of glioblastoma by interfering with tumor cell mitosis at anaphase. Results from a Phase III clinical trial indicate that the efficacy of NovoTTF-100A is equivalent to standard-of-care chemotherapy. The side effect profile favors device-treated patients, obviating typical toxicities associated with chemotherapy or targeted drugs, and results in improvements in their quality of life. NovoTTF-100A is a new modality of cancer treatment that offers equivalent efficacy, but less toxicity, to recurrent glioblastoma patients when compared with existing treatments.

Keywords: chemotherapy • electric field • glioblastoma • NovoTTF-100A • tumor-treating field

Overview of the market

Despite continuing research in drug treatments for glioblastomas, median patient survival remains a dismal 14.6 months from the time of initial diagnosis using combined radiation and chemotherapy [1]. Fewer than 10% of patients survive to the 5-year time point [2]. At the time of glioblastoma recurrence or progression, the overall survival (OS) of patients is even worse – typically 6 months or less [3]. The only US FDA-approved medical treatment for recurrence is bevacizumab, but this drug has never been tested in a Phase III clinical trial. Current salvage treatment with bevacizumab prolongs only the progression-free survival (PFS), but not OS, and the tumor invariably progresses in an infiltrative pattern, causing neurological deficits and eventual death [4,5]. Both bevacizumab and cytotoxic chemotherapies have serious side effects that include hemorrhage, thromboembolism, infection, hypertensive crisis, renal failure, diarrhea, nausea and vomiting [4–6]. Therefore, there is a great unmet need for novel therapies that have new mechanisms of action against glioblastoma and a more favorable toxicity profile.

Introduction

NovoTTF-100A (Novocure Inc., Haifa, Israel) is a novel class of therapeutic device being used

for the treatment of recurrent glioblastoma. It works by emitting low-intensity, intermediate-frequency (200 kHz), alternating electric fields administered by insulated transducer arrays to inhibit the growth and proliferation of intracranial glioblastomas [7]. This device, which consists of the transducer arrays, electric field generator (set at a frequency of 200 kHz) and battery (Figure 1), was approved for use by the FDA on 8 April 2011 [10]. This review summarizes its mechanisms of action, Phase III efficacy and safety data, and current use in clinical practice.

Mechanism of action

NovoTTF-100A exerts its anti-tumor effect on glioblastoma cells by interfering with mitosis at anaphase. In synchronized cell culture, such a tumor-treating electric field (TTField) first disrupted cytokinesis and then impaired chromosome separation from the metaphase plates [8]. Biochemical assays also confirmed that these cells had already transitioned from metaphase to anaphase [8]. Immunofluorescence of treated cells demonstrated lagging chromosomes, dispersion of chromosomes, chromosome decondensation in the absence of cytokinesis, and asymmetric chromosome segregation [8,9]. Exposed cells showed no p53 induction, suggesting that cell death was mediated via a p53-independent

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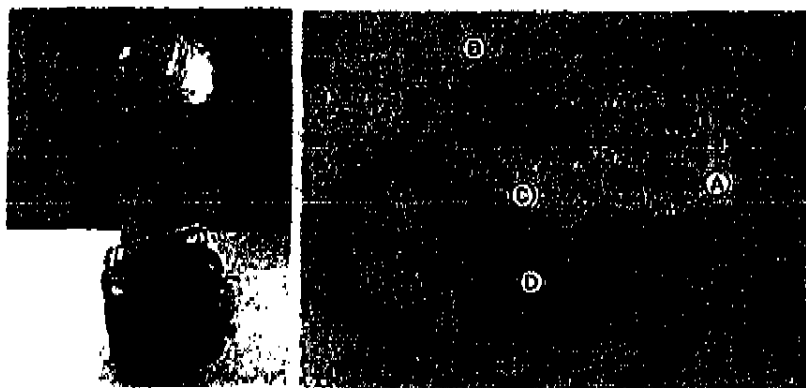


Figure 1. The NovoTTF-100A device setup. Left panel: The NovoTTF-100A device. Right panel: Two opposing pairs of transducer arrays (A) are applied to the scalp and the cables are linked to the connection box (B). The connection box is then attached to the electric field generator (C), which is connected to a power supply (D). The entire set up weighs approximately 7 lbs.

mechanism [8]. Furthermore, susceptibility to TTField is cell type dependent. Both glioma cells from rats (R-98) and humans (UB7 and U118) have a significantly decreased growth rate when exposed to TTField [9]. The best result appears to occur at an intensity of 2.25 V/cm and a frequency of 200 kHz [9]. Taken together, TTField represents a new modality of anticancer treatment via a mechanism that differs from conventional radiotherapy, cytotoxic chemotherapies or targeted kinase inhibitors. However, additional research is needed to determine the effect on postmitotic neurons and glia, as well as dividing progenitor cells, within the brain.

Clinical efficacy

NovoTTF-100A underwent initial testing in a pilot trial of ten patients with recurrent glioblastoma [7]. The results showed that the median time to disease progression was 26.1 weeks (range: 3.0–124.0 weeks), the PFS at 6 months (PPS6) was 50% (95% CI: 23–77%), and the median OS was 62.2 weeks (range: 20.3–124.0 weeks) [1]. There were two durable responses, including two patients with complete and partial responses lasting 43.3+ weeks and 30.3+ weeks, respectively [7]. These preliminary data compared favorably to benchmark outcomes from conventional cytotoxic chemotherapies, which had a response rate of 9%, PPS6 of 15%, median PFS of 9.0 weeks, and a median OS of 25.0 weeks (95% CI: 21–28 weeks) [3].

NovoTTF-100A was subsequently compared to best standard of care (BSC) chemotherapy for recurrent glioblastoma after initial temozolomide chemoradiation in a prospective, randomized, open-label Phase III clinical trial. Among the 28 centers in the USA and Europe, 237 individuals were randomized to NovoTTF-100A alone (120 subjects) or BSC (117 subjects) [10,11]. The primary end point was OS and secondary end points included PFS, PPS6, 1-year survival rate, objective radiological response, quality of life and safety. All analyses were performed on the intent-to-treat population, and Kaplan–Meier OS and PFS were computed from the time of randomization until event or censoring at last

follow-up. The trial was powered at 80%, with a significance of $p \leq 0.05$ and a hazard ratio (HR) for death of ≤ 0.67 . The median age, Karnofsky Performance Score and other clinical characteristics were balanced between the two cohorts, with the exception of slightly larger tumor size in the NovoTTF-100A group versus the BSC group, at a median size of 6.1 cm (range: 0.0–15.2 cm) and 5.5 cm (range: 0.0–16.2 cm), respectively (Table 1) [10,11]. BSC chemotherapies chosen by the treating physician included single-agent or combination irinotecan (31%), bevacizumab (31%), BCNU/CCNU (25%), carboplatin (13%), temozolomide (11%), combination procarbazine, CCNU and vincristine (9%), etoposide (3%), imatinib (2%), hydroxyurea (1%), or nothing (3%) [10,11]. In the intent-

to-treat population, the median OS was 28.6 versus 26.0 weeks (HR: 0.86; 95% CI: 0.66–1.12), the median PFS was 9.5 versus 9.1 weeks (HR: 0.84, 95% CI: 0.64–1.13), and the median PPS6 was 21 versus 15% for NovoTTF-100A and BSC chemotherapy, respectively (Figure 2) [10,11]. The data indicate that NovoTTF-100A has an equivalent efficacy when compared to salvage cytotoxic chemotherapies and targeted drugs for recurrent glioblastoma. Interestingly, patients who failed bevacizumab and then enrolled to receive NovoTTF-100A ($n = 23$) had a significantly longer survival than those who received BSC chemotherapy ($n = 21$), at 19.1 versus 13.4 weeks ($p < 0.02$), respectively [12].

Safety & tolerability

The side effect profile favors NovoTTF-100A treatment significantly more than BSC. Notably, there were only 3 versus 17% hematological toxicities, 4 versus 17% gastrointestinal side effects, and 4 versus 8% infections at grade 3 or 4 severity in the NovoTTF-100A versus BSC cohorts, respectively [10,11]. Other systemic toxicities were well-balanced between the two groups. However, scalp irritation from transducer array placement did occur at a higher frequency, with 17% grade 1 and 2 skin rash in the NovoTTF-100A subjects when compared with 0% in those treated with BSC chemotherapy [10,11]. However, none of the device-treated patients experienced skin toxicity higher than grade 2. Additional self-reported quality-of-life analysis by EORTC QLQ C-30 showed positive scores from NovoTTF-100A usage due to improved cognitive function, decreased constipation and diarrhea complications, as well as absence of pain [11,12].

Use in practice

Certain medical conditions are contraindicated in NovoTTF-100A usage and may pose unknown risks to patients. First, it is inadvisable to prescribe this device to patients with active implanted medical devices, such as cardiac pacemakers, defibrillators, deep-brain stimulators, vagus nerve stimulators and

NovoTTF-100A: a new treatment modality for recurrent glioblastoma

Patient Profile

Table 1. Baseline characteristics of subjects enrolled in the Phase III NovoTTF-100A trial for recurrent glioblastoma.

	NovoTTF-100A (n = 120)	Active control (n = 112)
Age, median (range)	54 (24–80) years	54 (29–74) years
Gender:		
– Male	92 (77%)	73 (62%)
– Female	28 (23%)	44 (38%)
Histology:		
– Primary glioblastoma	110 (92%)	108 (92%)
– Secondary glioblastoma	10 (8%)	9 (8%)
Karnofsky performance status, median (range)	80 (50–100)	80 (50–100)
Corticosteroid use at the time of enrollment:		
– Yes	55 (46%)	62 (53%)
– No	55 (46%)	49 (42%)
– Unknown	10 (8%)	6 (5%)
Maximum tumor diameter at randomization, median (range)	6.1 (0.0–15.2) cm	5.5 (0.0–16.2) cm
Time from initial glioma diagnosis, median (range)	11.8 (3.2–99.3) months	11.4 (2.9–77.1) months
First recurrence	11 (9%)	17 (15%)
Second recurrence	58 (48%)	54 (46%)
Third or greater recurrence	51 (43%)	46 (39%)
Surgery:		
– Debulking surgery prior to enrollment	33 (28%)	29 (25%)
– Debulking at any stage	95 (79%)	99 (85%)
– Biopsy only	25 (21%)	18 (15%)
Radiotherapy:		
– Radiotherapy with concomitant temozolomide	103 (86%)	96 (82%)
– Radiotherapy without concomitant temozolomide	15 (13%)	20 (17%)
– Unknown	2 (1%)	1 (1%)
Prior adjuvant (maintenance) temozolomide	100 (83%)	89 (76%)
Median number of cycles	4 (0–19)	3 (0–27)
Prior bevacizumab use	23 (19%)	21 (18%)

Data taken from [11].

programmable ventriculoperitoneal shunts. These devices may cause reciprocal electromagnetic interference, induction or both, and the extent of this risk is unknown. Second, patients with major skull defects cannot receive this treatment. For example, those with a missing section of the calvarium may experience elevated electric field strength on the brain. However, those with healed burr holes and craniotomy sutures can receive this treatment without complications. Third, metals within the brain are also contraindicated because NovoTTF-100A has not been tested in patients with bullet fragments or aneurysm clips in their head. Last, those with hypersensitivity to hydrogel, which is used as a

conductive interface between the transducer array disks and the scalp, may not be able to receive this treatment.

Pretreatment evaluation consists of baseline history, physical examination (including evaluation of skin integrity on the scalp), blood work and gadolinium-enhanced head MRI. The MRI images are used to construct a mapping diagram for placement of the transducer arrays. Typically, there are two pairs of opposing arrays, which are separately color coded (Figure 1). The wires of the arrays are then connected to the electric field generator and power supply (Figure 1). The patient's hair is then shaved off with an electric shaver instead of a razor in order to avoid superficial

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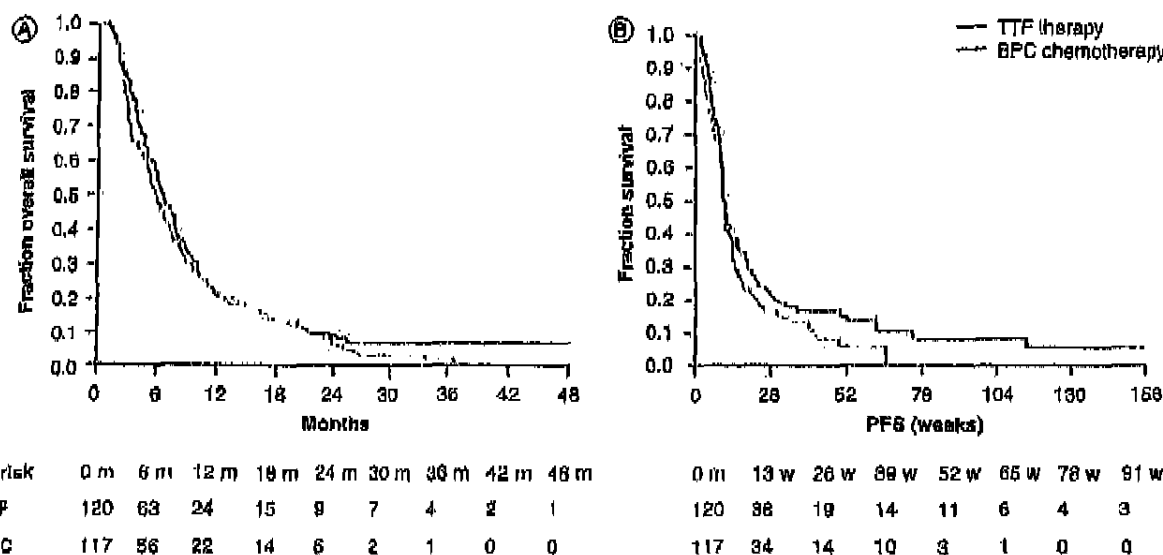


Figure 2. Data from a Phase III NovoTTF-100A trial for recurrent glioblastoma. (A) Kaplan-Meier curves showing equivalent overall survival between the NovoTTF-100A therapy group and the BPC active control. (B) Kaplan-Meier progression-free survival curves showing a greater number of subjects with disease stabilization in the NovoTTF-100A-treated group than BPC active control: four subjects without disease progression at 78 weeks and three at 91 weeks versus none in the control. BPC: Best physician choice; m: Months; PFS: Progression-free survival; w: Weeks. Reproduced with permission from [11].

cuts. The scalp is then cleaned with alcohol prior to application of the arrays. This procedure typically requires the help of another individual and it is necessary to bring a family member or assistant to learn array placement and operation of the NovoTTF-100A device. Follow-up clinic visits are scheduled monthly in the first 3 months and then every 2 months thereafter. Gadolinium-enhanced head MRI is performed once every 2 months for monitoring the status of glioblastoma during treatment.

The efficacy of NovoTTF-100A on brain tumors other than glioblastoma is unknown. However, other gliomas may respond to the same frequency (200 kHz) emitted by the NovoTTF-100A device, based on published preclinical data. However, it is still unknown whether or not TTFeld at 200 kHz would be effective in controlling metastatic brain tumors because the optimal frequency for specific metastasis may be different. For example, in preclinical cell culture melanoma was most sensitive at a frequency of 120 kHz [9].

Regulatory affairs

NovoTTF-100A is currently approved by the FDA and the EMA for the treatment of recurrent or progressive glioblastomas.

Conclusion

NovoTTF-100A is a novel therapy for the treatment of recurrent glioblastoma. It emits TTFeld that interferes with dividing tumor cells at anaphase. The clinical trial results indicate that it has comparable efficacy, and less toxicity, when compared to conventional drug treatments in the recurrence setting.

Expert commentary

The Phase III clinical trial demonstrated comparable, but not superior, efficacy when compared to conventional drug treatments. This result is likely to be influenced by a number of factors. First, the population of patients with recurrent glioblastoma has neurological deterioration and death within a shorter time than those with newly diagnosed disease. As a result, these patients may deteriorate early and therefore their tumors may not receive enough exposure to NovoTTF-100A treatment. Unlike conventional cytotoxic chemotherapies that have a biological effect lasting the entire duration of the treatment cycle (typically 4–6 weeks), the TTFeld needs to be applied continuously otherwise the anti-tumor effect would disappear as soon as the generator is switched off. Consistent with this reasoning, the per-protocol analysis of the Phase III trial data, in which patients who received less than 4 weeks of NovoTTF-100A treatment were removed from analysis, showed that NovoTTF-100A offered a statistically significant survival advantage when compared to BSC chemotherapy. Second, compared to newly diagnosed glioblastomas, recurrent glioblastomas have additional genetic alterations making them more resistant to treatment [13,14]. Therefore, NovoTTF-100A may have a greater benefit to newly diagnosed patients than those with recurrent disease. A Phase III clinical trial is currently underway investigating the efficacy of NovoTTF-100A with temozolomide chemoradiation compared to standard temozolomide chemoradiation for newly diagnosed glioblastoma. Last, NovoTTF-100A does not appear to have overlapping toxicity with conventional drug treatments [10,11]. Therefore,

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combining it with cytotoxic chemotherapies or targeted agents can potentially result in increased efficacy and without added toxicity. The pivotal Phase III trial did include patients after failure of polifeprosan 20 with carmustine implant (Gliadel wafer) (11). However, for patients who have undergone wafer implantation, it would be best to withhold the use of NovoTTF-100A until complete dissolution of the wafer, which typically occurs in 4 weeks. However, more preclinical data are needed in order to find the optimal NovoTTF-100A and drug combinations before they can be applied in a clinical trial setting.

Five-year view

In the next 5 years, more preclinical studies are needed in order to determine the mechanisms of TTField's action on tumor cells. The results would most likely offer ideas for investigator-initiated clinical research that would help to maximize the efficacy of NovoTTF-100A against glioblastomas. This will most likely

be accomplished by the addition of drugs that have synergistic or additive activities. A logical combinatorial treatment would include NovoTTF-100A and bevacizumab because these two therapies do not have overlapping toxicity and both are approved by the FDA for the treatment of recurrent glioblastomas. Furthermore, the device could also be used to treat patients with metastatic brain tumors. However, more preclinical and clinical research is needed to support its use in these patients, as well as the specific type of metastatic brain tumor that shows sensitivity to TTField.

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Key issues

- NovoTTF-100A (Novocure Inc., Haifa, Israel) emits a low-intensity, intermediate-frequency (200 kHz) alternating electric field that treats recurrent glioblastomas.
- NovoTTF-100A exerts its anti-tumor effect on glioblastoma cells by interfering with mitosis at anaphase.
- NovoTTF-100A treatment offers comparable efficacy when compared to conventional drug treatments, including bevacizumab, for recurrent glioblastoma.
- The toxicity profile favors NovoTTF-100A over conventional drug treatments.

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By Philip H. Gutin, MD, and Eric T. Wong, MD

Overview. Tumor treating fields (TTF) therapy is a novel noninvasive, electric field-based treatment for cancer. This nonchemical, nonablative treatment is unlike any of the established cancer treatment modalities, such as surgery, radiation, and chemotherapy. Recently, it has entered clinical use after a decade of intensive translational research. TTF therapy is delivered to patients by a portable, battery-operated, medical device using noninvasive transducer arrays placed on the skin surface surrounding the treated tumor. TTF therapy is

now a U.S. Food and Drug Administration (FDA)-approved treatment for patients with recurrent glioblastoma (GBM) who have exhausted surgical and radiation treatments. This article will introduce the basic science behind TTF therapy, its mechanism of action, the preclinical findings that led to its clinical testing, and the clinical safety and efficacy data available to date, as well as offer future research directions on this novel treatment modality for cancer.

THE DEFINITION of the electric field is attributed to Michael Faraday in the 1820s and was later formulated by James Clerk Maxwell in his electromagnetic theory in 1866.¹ It is a field of electric forces that surround a source charge. When a test charge is placed within an electric field, a force acts on it. Negative charges attract positive charges, while similar signed charges repel each other. As seen in Fig. 1A, an electric field surrounding a source charge can be described using diverging lines of force. The closer the test charge is to the source charge, the closer the lines of force are to each other, which represents higher field intensity.

To understand the effects of electric fields within cells, it is important to introduce three definitions. First, electric fields can be uniform or nonuniform. A uniform electric field is represented by parallel lines of force (Fig. 1B). A nonuniform electric field is represented by converging or diverging lines of force (Fig. 1A and 1D). Second, an electric field can be a constant field or a time-varying field, resulting in electrostatic or electrodynamics phenomena, respectively. In a constant field, the source charges remain the same over time. A test charge will move in one direction within a constant electric field toward the oppositely charged source (Fig. 1B). In a time-varying or alternating electric field, the charge of the sources alternates over time (Fig. 1C). Third, the test charge can be an electric charge or an electric dipole (an element with a positive charge on one end and a negative charge on the opposite end). An electric charge will move back and forth, while a dipole will rotate within an alternating uniform electric field and align with the direction of the field. In a nonuniform converging electric field, both dipoles and charges move in the direction of the higher field intensity through a process known as dielectrophoresis (Fig. 1D).

Mechanism of Action of TTF Therapy

Over 100 years after Maxwell's original publication, Yoram Palti, MD, PhD, hypothesized that properly tuned alternating electric fields at physiological intensities (i.e., 1–3 V/cm) would disrupt the mitotic process of dividing cancer cells.^{2,3} Dr. Palti hypothesized and subsequently demonstrated in vitro that at frequencies between 100 and 300 kHz, alternating electric fields disrupt the formation of the mitotic spindle during metaphase and lead to dielectrophoretic movement of charged and/or polar molecules and organelles during anaphase and telophase, disrupting normal cytokinesis and leading to apoptosis.^{2,3} According to this model, the first mechanism of action is explained by the fact

that the tubulin subunits are one of the most polar molecules in the cell. These tubulin subunits align in the direction of the applied electric field (Fig. 2A), interfering with the normal polymerization of the mitotic spindle, which results in formation of abnormal mitotic figures in vitro.³ The second mechanism of action is explained by examining the change in shape of the electric field within a dividing cell from anaphase to telophase. When the cell division axis is aligned with the direction of the electric field, the field lines that enter the cell at one end converge at the cytokinetic furrow between the developing daughter cells and then diverge on the opposite side (Fig. 2B). This nonuniform electric field within the cell generates dielectrophoretic forces that act on polar and charged elements in the cell, pushing them toward the cytokinetic furrow leading to violent blebbing of the plasma membrane.³ This finding was also validated by researchers from Beth Israel Deaconess Medical Center and may be mediated by improper placement of the contractile elements that form the cytokinetic ring on anaphase entry.⁴

Preclinical Studies of the Antitumor Effects of TTF Therapy

Between 2004 and 2010, a series of publications and conference presentations addressed the issue of the applicability range of TTF therapy to different in vitro and in vivo cancer models either alone or in combination with standard chemotherapy.^{2,5–8} Tables 1 and 2 summarize the state-of-the-art preclinical research with TTF therapy. TTF therapy has been shown to effectively inhibit cancer cell growth in various cell lines in vitro (Table 1). This effect was clearly dose (field intensity) dependent in the range of 1 to 3 V/cm.⁹ The optimal frequency for the inhibitory effect of TTF therapy differed between cell types and was inversely related to cell size (Table 1; e.g., glioma cell cultures at 200 kHz^{3,6}). In addition, based on the directional nature of TTF

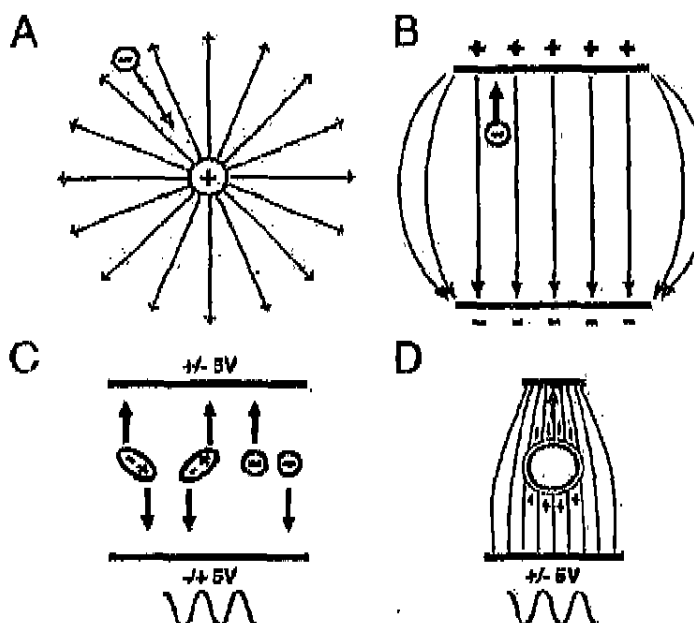
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Fig. 1. Electric field theory. (A) Opposite charges attract. (B) A constant, uniform, electric field. (C) Charges and dipoles in a time-varying, uniform electric field. (D) A dipole in a time-varying, nonuniform electric field (dielectrophoresis).



therapy, its antimetabolic effect in cultures was enhanced by sequentially applying more than one field direction to the treated cells.⁶ The combination of TTF therapy with different chemotherapeutic agents has been shown to have at least additive if not synergistic effects.^{7,8} Specifically, the combination of TTF therapy with temozolomide in glioma cell lines was shown to be additive. Interestingly, in breast cancer cells, TTF therapy showed overt synergism with taxanes (e.g., paclitaxel), probably a result of the temporal

proximity of taxanes' effect in metaphase and TTF therapy's mitotic interference on cell entry into anaphase.⁹

TTF therapy has been tested in numerous *in vivo* cancer models (Table 2).^{5,6,8,10} Noninvasive application of TTF therapy to animals was performed using electrically insulated transducer arrays placed on the head or torso surrounding the region of the tumor. Inhibition of tumor growth was seen in each of these models when the correct frequency of TTF therapy was applied. Specifically, 200 kHz TTF therapy applied in two sequential and perpendicular field directions lead to significant ($p < 0.01$) inhibition of a syngeneic, orthotopic F-88 glioma in rats after 7 days of treatment.⁶ An additional syngeneic, orthotopic model of non-small cell lung cancer in mice showed that 180 kHz TTF therapy significantly ($p < 0.01$) inhibited tumor growth within 7 days of treatment.^{10,11} Furthermore, the additive effect of TTF therapy with chemotherapy seen *in vitro* was recapitulated in different *in vivo* models.^{5,8} Finally, in a metastatic tumor model using a squamous carcinoma tumor implanted in the kidney capsule of rabbits, TTF therapy applied to the abdomen blocked metastatic spread of tumor from the kidney to the lungs.^{10,17}

Translating TTF Therapy into Clinical Use

Since TTF therapy is a physical antimetabolic modality with no half-life, its application should be continuous. Kinetic modeling was used to predict the minimal treatment duration needed with TTF therapy.¹⁸ Based on these data, a minimal treatment course of 4 weeks was defined and implemented in clinical studies. *In vivo* animal experiments and pilot clinical data subsequently verified the 4-week minimal treatment duration.¹⁸ Such continuous delivery was made possible by the development of a portable, battery-operated, medical device that patients can use at home (NovoTTF-100A, Novocure, Haifa, Israel). Finally, extensive toxicity studies of TTF therapy were performed in healthy

KEY POINTS

- Tumor treating fields (TTF) therapy is an emerging, low-toxicity treatment modality for solid tumors based on the delivery of antimetabolic alternating electric fields to the tumor, which interfere with cytodinesis and microtubule assembly that eventually lead to cell death.
- As a monotherapy, TTF therapy is at least as effective as currently available active chemotherapy and biologic therapies for the treatment of recurrent glioblastoma (GBM).
- The efficacy of this noninvasive treatment modality is achieved with significantly less toxicity and a better quality of life compared with chemotherapy.
- Preliminary data suggest TTF therapy acts synergistically with temozolomide and other chemotherapy in both preclinical and clinical trials.
- Future research should focus on integrating TTF therapy into the treatment of GBM in the adjuvant and maintenance settings, as well as in the treatment of other solid tumor malignancies.

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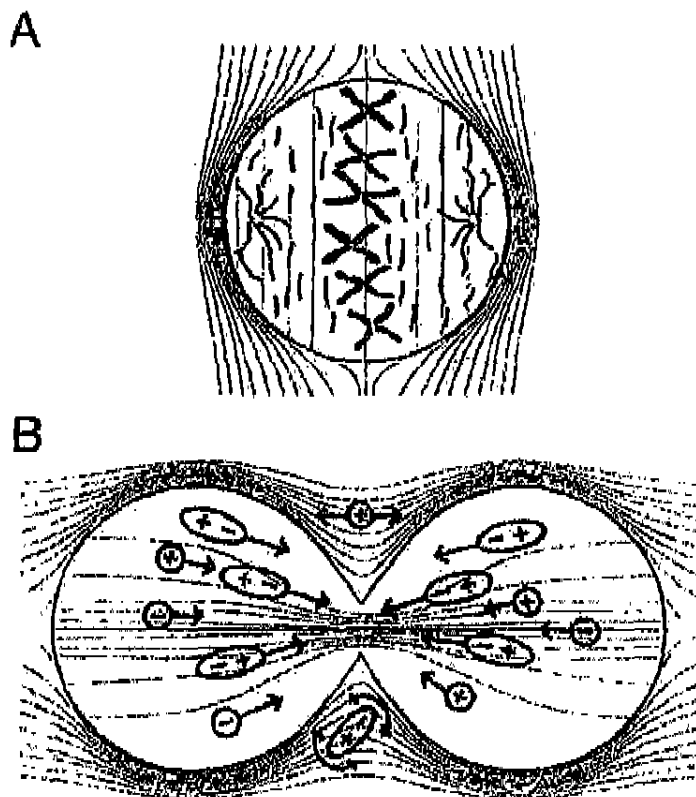


Fig. 2. Effects of tumor treating fields therapy on intracellular structures during mitosis. (A) During metaphase, tubulin dimers align with the external electric field, interfering with the formation of the mitotic spindle. (B) During cytokinesis, the nonuniform electric field formed within the dividing cell drives charged and polar macromolecules, and organelles toward the cleavage furrow.

mice, rats, and rabbits.^{5,9} Clinical, laboratory, and pathologic analyses showed that TTF therapy is well tolerated and does not lead to systemic toxicity in animals. As expected by the frequency range of TTF therapy (100–800 kHz), these electric fields do not have any effect on excitable tissues (neural, muscular, or cardiac), nor do they cause significant heating.^{18–15}

Clinical Testing of TTF Therapy as a Monotherapy

The NovoTTF device was first applied to patients in a small feasibility trial in Switzerland in 2000.¹⁶ In 2004, TTF therapy was tested in a pilot clinical trial in patients with recurrent GBM (Table 2).⁵ This single-center, single-arm trial included patients with favorable prognostic character

Table 1. In Vitro Evidence Overview

Histology	Cell line	Optimal/Effective TTF Frequency (kHz)	Additive/Synergistic with Chemotherapy	Reference
High-grade glioma	P-98; C-6; RG-2 U-118; U-87	200	Temozolomide (temozolomide)	Can Res, 2004 ³ Proc Natl Acad Sci U S A, 2007 ⁹
Breast adenocarcinoma	Normal: MDA-MB-231 MCF7	120	Cyclophosphamide	Can Res, 2004 ³
	Multidrug resistant: MDA-MB-231/Dox AAB/Emr ⁺ MCF7/Mx	120	Doxorubicin Paclitaxel	Neuro Oncol, 2011 ⁴ DMC Cancer, 2010 ⁷
Non-small cell lung cancer (adenocarcinoma)	H1299 LLC	150	Doxorubicin Paclitaxel Pemetrexed	ERS, 2010 ⁸ AACR, 2007 ⁶ Can Res, 2004 ³
Colorectal adenocarcinoma	CT-26	100*	NA	Can Res, 2004 ³
Malignant melanoma	B16F1/Petriola	100	NA	Can Res, 2004 ³
Prostate	PC-3	100*	NA	Can Res, 2004 ³
Cervical cancer	Hela	200*	NA	Neuro Oncol, 2011 ⁴

Abbreviations: TTF, tumor treating fields; NA, not available (was not reported by the authors).

* Effect seen at this frequency; additional frequencies were not tested.

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Table 2. In Vivo Evidence Overview

Tumor Type	Anatomic location	Animal Model	Frequency (Hz)	Effect of TTF	References
GBM	Right hemisphere	Rat	200	Tumor growth inhibition with 2 and 3 field directions	<i>Proc Natl Acad Sci U S A</i> , 2007 ³
Non-small cell lung cancer	Lung parenchyma	Mouse	150	1. Tumor growth inhibition with 2 field directions 2. Additive tumor inhibition with pemetrexed	<i>ERS</i> , 2010 ⁸
Malignant melanoma	Intradermal	Mouse	100	Tumor growth inhibition with 1 and 2 field directions	<i>Carc Res</i> , 2004 ³ <i>Proc Natl Acad Sci U S A</i> , 2007 ³
Malignant melanoma	Intravenous	Mouse	100	Inhibition of metastatic seeding in the lungs	<i>Clin Exp Metastasis</i> , 2009 ¹⁰
VX-2 (papilloma)	Kidney capsule	Rabbit	150-200	1. Tumor growth inhibition seen with 2 field directions 2. Increase in median survival 3. Inhibition of metastatic seeding in the lungs 4. Additive tumor inhibition with pemetrexed	<i>Clin Exp Metastasis</i> , 2009 ¹⁰ <i>AACR</i> , 2009 ²⁷ <i>Neuro Oncol</i> , 2010 ¹²

Abbreviation: GBM, glioblastoma

istics. Treatment with the device was well tolerated, and no treatment-related serious adverse events were reported. Most patients developed grade 1 to 2 contact dermatitis beneath the transducer arrays on the scalp. Efficacy endpoints were very encouraging with a 20% objective response rate, progression-free survival (PFS) at 6 months of 60%, median time to progression (TTP) of 26 weeks, and median overall survival (OS) of 62.2 weeks (14.4 months). Compared to the historic results of salvage chemotherapy, these results showed clear activity of TTF therapy when used as a monotherapy in recurrent GBM.¹⁷

Based on the results of this pilot trial, a pivotal phase III, multicenter, randomized (1:1) clinical study was initiated in patients with recurrent GBM (Table 3). The randomized study, which recruited 287 patients between 2008 and 2009, compared the efficacy and safety of monotherapy with the NovoTTF device to that of the best available active chemotherapy according to physician's choice. Thirty-six patients received bevacizumab, 36 received nitrosourea, 12 received temozolomide, and 33 received other agents. This was the largest randomized study in recurrent GBM to be completed to date. The results of the study were presented at the 2010

ASCO Annual Meeting and were updated at the 2011 Society for Neuro-Oncology (SNO) Annual Meeting.^{18,20} Baseline characteristics of patients were balanced between the two treatment groups. In both groups, patients had poor prognostic predictors compared with previous clinical trials of recurrent GBM (90% of patients were at their second or subsequent recurrence; 20% had failed bevacizumab before entering the trial; and the average tumor diameter was above 5 cm). In the conservative intent-to-treat (ITT) analysis, the study showed that patients with recurrent GBM treated with NovoTTF alone had comparable OS to that of patients who received chemotherapy and/or bevacizumab (3.6 months vs. 6.0 months; respectively; $p = 0.26$; hazard ratio [HR] = 0.86; Table 3). Although NovoTTF did not show superiority over active chemotherapies, it was clear that it was at least as effective as these treatments. Secondary endpoints in the trial were supportive; blinded radiology review showed that PFS at 6 months was 21.4% in the NovoTTF group compared with 15.2% in the chemotherapy group ($p = 0.24$). There were more radiological responses even in the NovoTTF group compared with the chemotherapy group (12% vs. 8%, respectively; $p = 0.07$), including

Table 3. Clinical Evidence Overview

Indication (Analysis Group)	Trial Phase (# of Subjects) Analysis	Overall Survival (Months)		Hazard Ratio (p)	Progression-Free Survival (PFS) at 6 Months or Median PFS (Weeks)		P value	References
		TTF	Chemo		TTF	Chemo		
Recurrent GBM (at first relapse)	Phase I-II (n = 10) ITT Analysis	14.5 m	6.0 m*	Non-randomized	50%	15%*	NA	<i>Proc Natl Acad Sci U S A</i> , 2007 ³
Recurrent GBM (at second and fourth relapse)	Phase III (n = 237) ITT analysis	6.6 m	6.0 m	HR = 0.86 ($p = 0.26$)	21.4%	15.2%	$p = 0.24$	<i>J Clin Oncol</i> , 2010 ¹⁸ <i>Neuro Oncol</i> , 2011 ¹⁹
Recurrent GBM (treated patients only)	Phase III (n = 210) PP Analysis	7.8 m	6.0 m	HR = 0.67 ($p < 0.012$)	26.2%	15.2%	$p = 0.03$	<i>J Clin Oncol</i> , 2010 ¹⁸ <i>Neuro Oncol</i> , 2011 ¹⁹
Recurrent GBM (KPS \geq 80, age $<$ 61)	Phase III (n = 110) Subgroup analysis	8.3 m	6.6 m	HR = NA ($p < 0.01$)	25.6%	7.7%	NA	<i>Neuro Oncol</i> , 2010 ¹⁹
Recurrent GBM (after bevacizumab failure)	Phase III (n = 43) Subgroup analysis	4.4 m	3.1 m	$p = 0.02$	NA	NA	NA	<i>Neuro Oncol</i> , 2010 ²⁰
Recurrent GBM (TTF versus bevacizumab)	Phase III (n = 156) Subgroup analysis	6.6 m	5.0 m	HR = 0.65 ($p = 0.048$)	21%	21%	$p > 0.05$	<i>Neuro Oncol</i> , 2011 ²¹
Newly diagnosed GBM (together with temozolomide)	I-II (n = 10) ITT Analysis	39+ m	14.7 m*	($p = 0.002$)	90%	50%*	NA	<i>BMC Med Phys</i> , 2009 ⁸
Relapsed advanced NSCLC (together with pemetrexed)	I-II (n = 42) ITT Analysis	13.8 m	8.2 m*	NA	15% w	24 w		<i>ESMO</i> , 2010 ²² <i>ERS</i> , 2010 ⁸ <i>Expert Opin Investig Drugs</i> , 2010 ¹¹

Abbreviations: GBM, glioblastoma; ITT, intention to treat; NA, not available (was not reported by the authors); HR, hazard ratio; PP, per protocol; KPS, Karnofsky performance status; TTF, tumor treating fields; NSCLC, non-small cell lung cancer.

* Single-arm trials with literature control

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three sustained complete responses in the NovoTTF group compared with none in the chemotherapy group. These results were accompanied by significantly ($p < 0.05$) less treatment-related adverse events with NovoTTF compared with chemotherapy. Patients in the NovoTTF group reported a higher quality of life compared with patients treated with chemotherapy. This analysis was based on the European Organisation for Research and Treatment of Cancer QLQ-C30 and mirrored the lack of chemotherapy-related toxicities in the NovoTTF group. Interestingly, patients in the NovoTTF group reported better cognitive and emotional functioning and much less pain than patients in the chemotherapy group, although these domains of the questionnaire are not related to known side effects of chemotherapy.

The data, several exploratory analyses of the study data have been performed. The first analysis compared patients who received the same "amount" of therapy in both groups. This prospectively defined per-protocol analysis excluded patients from both groups who received less than one pre-defined treatment course. The analysis demonstrated superior survival in the NovoTTF group compared with the chemotherapy group (7.8 months vs. 6.0 months; $p = 0.012$, HR = 0.67).^{16,20} The rationale behind this analysis is that TTF is a physical modality with no half-life, so that the moment the therapy is stopped, its antimitotic effect stops as well. In contrast, chemotherapies have measurable plasma and tissue half-life, which results in continued efficacy and toxicity long after a dose has been given. Therefore, to achieve pharmacokinetic balance in the "amount" of treatment in both groups, this analysis used a simplified criterion that one course of chemotherapy (e.g., 1 day of carbustine or 5 days of temozolomide) is equivalent to four weeks of continuous TTF therapy.

Two more analyses of the study data were presented at the 2010 and 2011 SNO Annual Meetings.^{20,21} The first study analyzed known clinical prognostic factors of age and Karnofsky performance status (KPS). This analysis demonstrated that in patients age 60 and younger with a KPS greater than 70, treatment with NovoTTF resulted in superior OS compared with chemotherapy (8.8 months vs. 6.6 months; $p < 0.01$). This survival advantage could be attributed to better compliance with TTF therapy in this group of patients. In support of this finding, a statistically significant correlation was seen in the NovoTTF group between treatment compliance (as measured by the device computerized log file) and OS ($p = 0.0475$).

The second analysis is a post hoc, exploratory analysis of the treatment of 120 patients with NovoTTF compared with 86 patients with bevacizumab. Although without a prespecified analysis in the trial, patients in the study treated with NovoTTF lived significantly longer than those treated with bevacizumab (6.6 months vs. 5.0 months, respectively; $p = 0.048$, HR = 0.65).²¹ This analysis included all TTF patients who received either bevacizumab or NovoTTF. Patient characteristics were almost identical and, in fact, favored the bevacizumab group prognostically. Clearly, this analysis cannot be taken as final evidence of superiority of NovoTTF over bevacizumab; however, it should be treated as hypothesis-generating data for future clinical studies. Finally, in the 43 patients who entered the study after bevacizumab therapy failure (approximately 20% of patients in both groups), OS was significantly longer with TTF therapy

than with chemotherapy (4.4 months vs. 3.1 months, respectively; $p = 0.02$). The data for the chemotherapy-treated group is in line with previous publications, which showed that following bevacizumab failure, the survival of patients with recurrent GBM is limited.²²

Based on the results of this pivotal phase III study, the FDA approved the NovoTTF-100A device on April 8, 2011, through the premarket approval (PMA) regulatory pathway. The PMA pathway is reserved for class III (high-risk) medical devices and requires preclinical, clinical, and manufacturing evidence, including review of both efficacy and safety data by a panel of independent experts. The FDA concluded that the study results showed NovoTTF to be comparable in efficacy to active chemotherapy, without many of the side effects associated with chemotherapies and with a better quality of life.²³

Clinical Trials Evaluating TTF Therapy in Combination with Chemotherapy

Two studies of combined TTF therapy and chemotherapy have been published to date. The first was a single-arm, single-center trial performed in 2008 in patients with newly diagnosed GBM.²⁴ Patients received the Stupp protocol with TTF therapy added to maintenance temozolomide.²⁴ This trial showed promising PFS and OS data (PFS > 14 months; OS > 89 months; Table 3) and served as the basis for an ongoing, multicenter, pivotal phase III, randomized clinical study comparing TTF therapy and temozolomide with temozolomide alone in the maintenance stage of the Stupp protocol.

The second study tested TTF therapy together with pemetrexed in 42 patients with pretreated, advanced non-small cell lung cancer.^{21,25} Efficacy and safety with this combined treatment paradigm were promising. Time to local disease progression in the lungs and liver (where TTF was applied) was 23 weeks, and OS was 13.8 months. In contrast, TTF and OS for pemetrexed alone were previously reported to be 12 weeks and 6.3 months, respectively.²⁶

TTF therapy is still in its early days. However, it has an established mechanism of action, and a growing body of preclinical evidence has shown its wide applicability in solid tumor malignancies either alone or in combination with standard chemotherapies. Objective antitumor activity and an unprecedented safety profile of this treatment modality have been seen in patients with recurrent GBM. Although TTF monotherapy has been shown to be at least as effective as the best available chemotherapies today for recurrent GBM, in-depth analysis of the phase III study data identified at least two subgroups where TTF therapy was superior to chemotherapy and could be offered to patients as an alternative to chemotherapy: younger patients with a better functional status and patients in whom bevacizumab treatment has failed in the past.

Conclusion

The approval of TTF therapy for recurrent GBM ushers in a fourth modality of cancer treatment. More importantly, TTF treatment has a superior safety profile, and its minor side effects do not appear to overlap with those of cytotoxic chemotherapies, targeted agents, or antiangiogenesis drugs. Therefore, the rational combination of TTF therapy with specific pharmacologic agents may enhance tumor cell death

TTF THERAPY IN GLIOBLASTOMA

because of potential additive or synergistic effects. First, as demonstrated in preclinical and clinical models, chemotherapy administered together with TTF therapy may result in additive or synergistic tumor control without increasing systemic toxicities. Second, TTF treatment could be combined with targeted agents that block survival signaling within the tumor cell. This block may be sufficiently strong to enhance the cytotoxic effect of TTF therapy or vice versa.

Third, the combination of TTF and antiangiogenesis agents may be another promising path that combines different antitumor treatments to improve tumor control. Lastly, the proper scheduling of TTF therapy with other agents is unknown. Additional research may shed light on the optimal scheduling that may achieve a synergistic effect on tumor growth leading to long-term tumor control and enhanced patient survival.

Authors' Disclosures of Potential Conflicts of Interest

Author	Employment or Leadership Positions	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors

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We have recently shown that low intensity, intermediate frequency, electric fields inhibit by an anti-microtubule mechanism of action, cancerous cell growth *in vitro*. Using implanted electrodes, these fields were also shown to inhibit the growth of dermal tumors in mice. The present study extends these findings to additional cell lines [human breast carcinoma (MDA-MB-231, and human non-small-cell lung carcinoma (H1299)] and to animal tumor models (intradermal B16F1 melanoma and intracranial F-98 glioma) using external insulated electrodes. These findings led to the initiation of a pilot clinical trial of the effects of TTFields in 10 patients with recurrent glioblastoma (GBM). Median time to disease progression in these patients was 26.1 weeks and median overall survival was 62.2 weeks. These time to disease progression and OS values are more than double the reported medians of historical control patients. No device-related serious adverse events were seen after >70 months of cumulative treatment in all of the patients. The only device-related side effect seen was a mild to moderate contact dermatitis beneath the field delivering electrodes. We conclude that TTFields are a safe and effective new treatment modality which effectively slows down tumor growth *in vitro*, *in vivo* and, as demonstrated here, in human cancer patients.

cancer | glioblastoma | tumor treating fields

Because living cells consist of ions, polar or charged molecules, membranes, and organelles, they are responsive to and often generate electric fields and currents. The electric activity of cells plays a key role in many essential biological processes. The electric fields associated with all of the above phenomena are in the range of 0–10 V/cm, except within cell membranes (1) where they may reach 10^3 V/cm. Whereas electric fields induce ion flow, polar molecules only orient themselves along the lines of a uniform field (2). However, nonuniform electric fields exert forces on polar molecules forcing them to move toward higher field intensity, a well known process known as dielectrophoresis (3, 4). Electric fields and resulting currents, when sufficiently large, stimulate nerves, muscles, cardiac muscle, etc. Only much larger fields generate heat that may damage cells (5).

In an electric field of alternating direction (ac field) all charges and polar molecules are subjected to forces of alternating direction so that ionic flows and dipole rotation oscillate (Fig. 1). In view of the relatively slow kinetics of the bioelectrical responses, as the ac fields' frequency is elevated, their biological effect (except for heating) is reduced such that, >10 kHz, it becomes negligible. Therefore, it is generally believed that ac fields of 100 kHz or above have no meaningful biological effects (5), although a number of nonsignificant effects have been described (6–8).

In contradiction to this belief, we have recently demonstrated (9) that 100 kHz to 1 MHz ac fields have significant specific effects on dividing cells. The basis of these effects during cytokinesis was shown to be the unidirectional forces induced by

the inhomogeneous fields at the bridge separating the daughter cells (Fig. 1B) that interfere with spindle tubulin orientation and induce dielectrophoresis.

It is the aim of this work to further study the effects of ac fields on quiescent and proliferating cells in culture, animal cancer models, and cancerous tumors in humans. Following a basic work on cell cultures (9), we demonstrate here that such fields, termed tumor treating fields (TTFields), are effective when applied by insulated external electrodes to animal cancer models and patients with recurrent glioblastoma (GBM). In a pilot clinical trial conducted on this extremely malignant tumor of glial cell origin (10, 11), TTFields treatment was found to be both safe and effective in slowing tumor progression. These promising results raise the possibility that TTFields could become a new treatment modality for cancer.

Cells in Culture

The effects of a 24-h exposure of four of the most common types of cancer [malignant melanoma, glioma (part of the data for malignant melanoma and glioma cells was taken from ref. 9), breast carcinoma, and non-small-cell lung carcinoma to TTFields] are illustrated in Fig. 2. It is seen that the number of unexposed (control) cells roughly doubles every 24 h, whereas the proliferation rate of the exposed cells is slowed down during exposure and gradually recovers after treatment is terminated (Fig. 2A). The frequency dependency of the effects is depicted in Fig. 2B. It is seen that the optimal frequency is 100 kHz for mouse melanoma (B16F1), 150 kHz for human breast carcinoma (MDA-MB-231), and 200 kHz for rat glioma (F-98). In addition, similar experiments were performed in two human glioma cell lines (U-118 and U-87). In both, the optimal TTFields frequency was identical to rat glioma cell lines (i.e., 200 kHz).

The "dose-response curve," i.e., the relationship between the TTFields effects and field intensity, is given in Fig. 2C. It is seen that effect on cell division and cell death (by apoptosis) is intensity dependent, the sensitivity being highest for mouse

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Conflict of interest statement: Y.P. has a minority holding in NovoCure Ltd. and is a member of the company board of directors. E.D.K., A.L., D.M., S.S.S., Z.G., R.S., and Y.W. are employed in full or part by NovoCure Ltd., and M.S. is a clinical trial consultant to NovoCure Ltd.

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Abbreviations: FEM, finite element mesh; GBM, glioblastoma; OS, overall survival; PFS, progression-free survival at 6 months; TTFields, tumor treating fields; TTP, time to disease progression.

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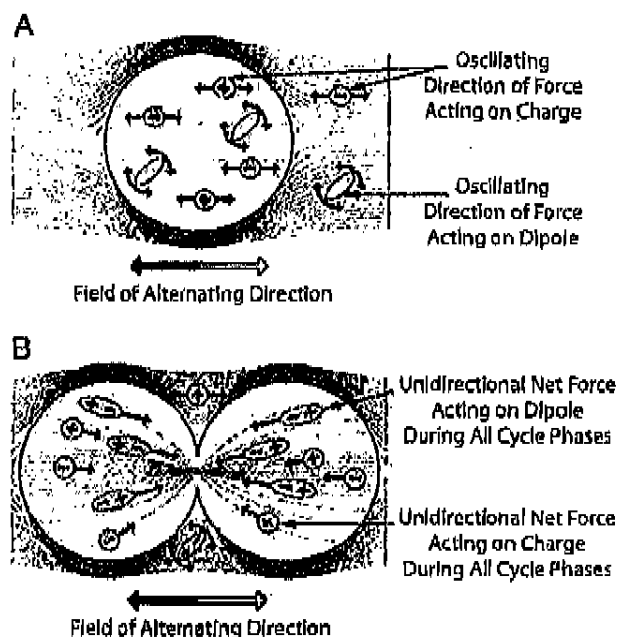


Fig. 1. Electric field distribution in and around quiescent (A) and dividing (B) cells. Inside quiescent cells, the field is uniform, and the oscillating electric forces result only in "vibration" of ions and dipoles (the forces associated with each half cycle are denoted white and gray arrows). In contrast, the nonuniform field within dividing cells (B) induces forces pushing all dipoles toward the furrow. Note that at frequencies of 0.1–1.0 MHz, the cell membrane impedance is relatively high, so only a small fraction of the currents penetrate the cells as seen from the density of lines.

melanoma cells, decreasing for rat glioma and for human non-small-cell lung carcinoma and lowest for human breast carcinoma.

From the mechanism of action of TTFields, as illustrated in Fig. 1, it can be deduced that their efficacy must be a function of the angle between the field and axis of division; when the two are parallel its maximal and when one is perpendicular to the

other, it must be minimal. Because in culture the axis of division is randomly oriented, only a fraction of the dividing cells are subjected to optimal treatment. To overcome this problem, multiple field directions were applied sequentially every 0.25–1 sec. Two perpendicular fields were found to be ~20% more effective than the single-direction one for B16F1 and F-98 cells. This result is consistent with the previously reported effects on malignant melanoma cells (9).

Animal Tumor Models

Intracranial Glioblastoma. Our report (9) described the effects of TTFields applied by means of implanted electrodes to intracranial malignant melanoma in mice. This report compares 40 Fischer rats inoculated intracranially with glioma cells, treated by means of external electrodes with a temperature- and geometry-matched electrode control group. The treatment duration was 6 days, using the optimal frequency of 200 kHz (see Fig. 2) at 2 V/cm. Fig. 3 depicts the computed field distribution in the rat brain (Fig. 3A), exemplary posttreatment MRI images of a control (Fig. 3B) and a treated tumor (Fig. 3C). The maximal diameter of the treated tumor is about half that of the control one.

The average inhibitory effect of unidirectional TTFields (in a temporal-temporal direction) was small and did not reach statistical significance (treated tumor volume 19.8% smaller than sham control tumors; $n = 26$; $P = 0.19$, Student's t test). However, increasing the number of TTFields directions caused statistically significant inhibition of tumor growth, reaching 42.6% and 53.4% for two ($n = 42$; $P < 0.01$, Student's t test) and three ($n = 10$; $P < 0.01$, Student's t test) directions positioned at 45–90° to each other, respectively.

Frequency Dependence of the Inhibitory Effect of TTFields. The TTFields inhibitory efficacy vs. frequency was studied on mice inoculated with B16F1 melanoma. The mice ($n = 26$) were treated for 5 days by single-direction TTFields of different frequencies. The maximal growth inhibition was found at 100 kHz, with the treated tumor size $62.7 \pm 8.9\%$ that of control tumors. Although this frequency dependence *in vivo* did not reach statistical significance (single-factor ANOVA, $P = 0.11$), it shows the same frequency dependency as the dependence of cultured B16F1 cells reported in ref. 9, which supports the

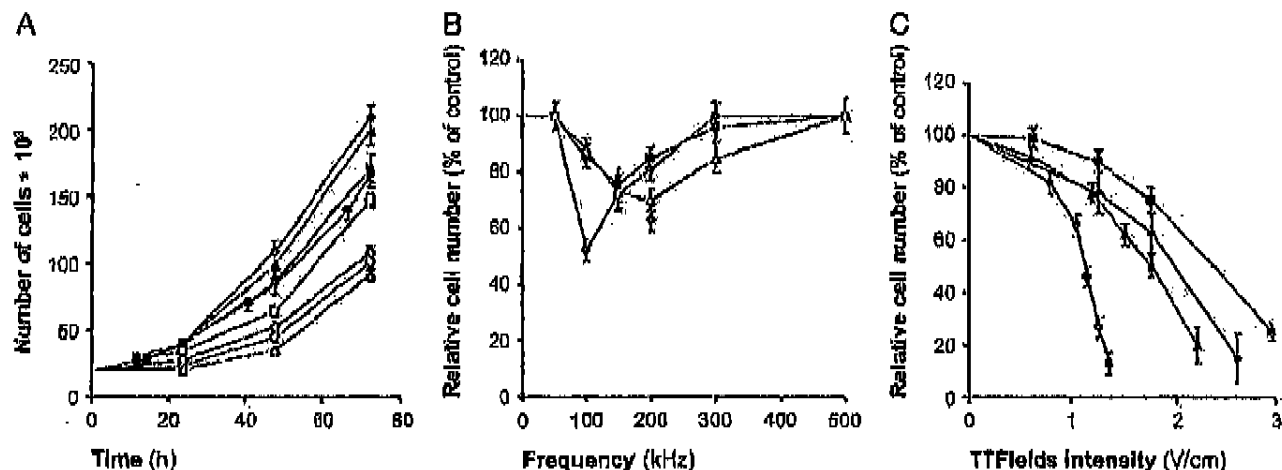


Fig. 2. Time, frequency, and intensity dependence of the effect of TTFields on cancer cell proliferation. (A) The number of cells in untreated cultures (filled symbols) as compared with cultures treated with TTFields (open symbols) for 24 h (1.75 V/cm for MDA-MB-231, F-98, and H1299 cells and 1.1 V/cm for B16F1 cells). (B) The relative change in number of cells after 24 h of treatment of different frequencies (same TTFields intensity). (C) The effect of 24 h of exposure to TTFields of increasing intensities (at optimal frequencies), ■ and □, B16F1; ■ and □, MDA-MB-231; ▲ and △, F-98; ◆ and ◇, H1299.

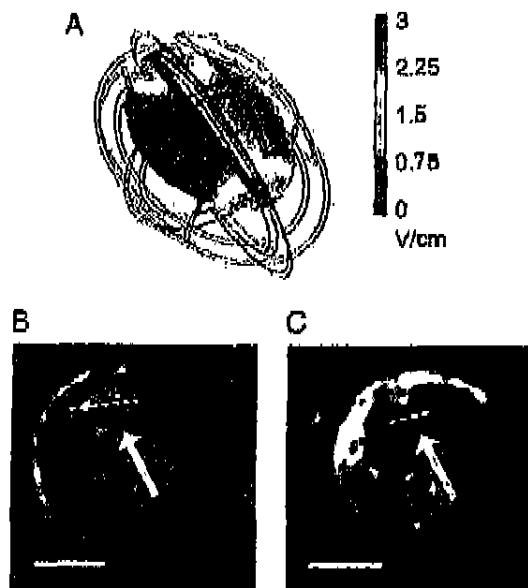


Fig. 3. TTFields inhibition of the growth of intracranial glioma. (A) FEM simulations (using a three-dimensional mesh) of the distribution of TTFields intensity within a simplified rat brain model. (B and C) Exemplary T1 weighted coronal MRI sections (after IV injection of Gd-DTPA) of the heads of a control and a TTFields treated (200 kHz, two-directional) TTFields rat, respectively. In both examples, the section shown is that with the largest diameter tumor. Head simulations are 3.1×1.9 cm ellipsoid; skin thickness, 0.4 mm ($\sigma = 0.00045$ S/m; $\epsilon = 1, 120$); skull thickness, 1.1 mm ($\sigma = 0.015$ S/m; $\epsilon = 16$); thickness of the CSF surrounding the brain, 0.5 mm ($\sigma = 2.5$ S/m; $\epsilon = 100$); and brain itself has the properties of a uniform white matter ($\sigma = 0.15$ S/m; $\epsilon = 3,200$). The electrodes placed over a 0.5-mm layer of hydrogel. Note the almost uniform field intensity in most brain volume. (Scale bars, 1 cm.)

conclusion that this is the optimum frequency. In contrast, rats bearing intracerebral glioma were unaffected by 100 kHz TTFields, whereas 200 kHz TTFields caused significant inhibition of tumor growth.

Safety Profile of TTFields in Healthy Animals. TTFields (100 kHz) at 6 V/cm were applied to the chest of three New Zealand rabbits. No changes were seen in the rate or regularity of cardiac rhythm

throughout and following the exposure. To test the safety of chronic TTFields application TTFields were applied to either the head ($n = 30$, 1 V/cm for 4 weeks) or the chest ($n = 10$, 9 V/cm for 2 weeks) of New Zealand Rabbits. All animals were assessed weekly for weight, temperature, BCG, CBC, wide chemistry panel and coagulation. After a 1-month follow-up period, all animals were killed and had samples of major organs examined by a pathologist. No treatment-related toxicities were recorded in any of the animals.

GBM Patients

TTFields Treatment of Patients with Recurrent GBM Brain Tumor. Ten patients with recurrent GBM were included in the trial (see *Materials and Methods* and supporting information (SI) Table 1).

As seen in Fig. 4A, the median time to disease progression (TTP) of the patients is 26.1 weeks (range 3–124 weeks) and the progression-free survival at 6 months (PFS6) is 50% (23–77%; 95% confidence interval). Two of the patients were still progression free at study closure.

The median overall survival (OS) of TTFields treated patients is currently 62.2 weeks (range 20.3–124.0 weeks). These TTP and OS values are more than double the reported medians of historical control patients. Three of the patients are still alive at this time. The Kaplan-Meier survival curve (12) of the treatment results is shown in Fig. 4B.

The TTFields treatment resulted in one complete response (Fig. 5A) which is still tumor free per MRI ten months after stopping treatment and one partial response (Fig. 5B) that is still responding 7 months after stopping treatment. Both are still progression free >2 years from treatment initiation. In addition one patient had minimal response and four had stable disease for over 4 months before progressing.

Safety Profile of TTFields Applied to GBM Patients. The 10 recurrent GBM Patients received treatment for a total of 280 weeks without a single treatment-related serious adverse event and no significant changes were seen in serum chemistry or blood count in any of the patients. The only changes seen consistently were elevated liver enzymes, attributed to anti-epileptic drug usage. Two patients had partial seizures that were unrelated to treatment. Nine of ten patients suffered from a mild to moderate contact dermatitis beneath the electrode gel. This treatment-related adverse event responded well to application of steroid creams and periodic electrode relocation.

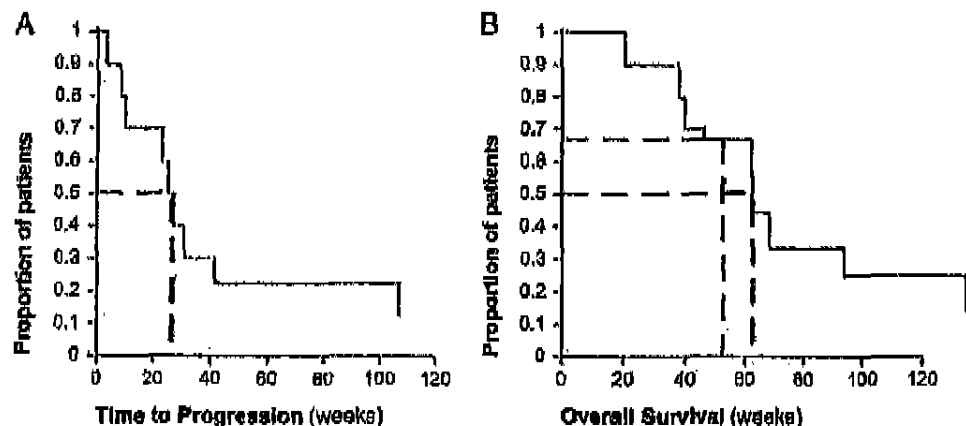


Fig. 4. Efficacy of TTFields treatment in recurrent GBM. (A) TTP of treated patients ($n = 10$); median TTP is 26.1 weeks (dashed black line). (B) Kaplan-Meier OS curve for NovoTT-100A treated patients ($n = 10$). The median OS in these patients is 62.2 weeks (black dashed line), and the 1-year survival rate is 57.5% (blue dashed line).

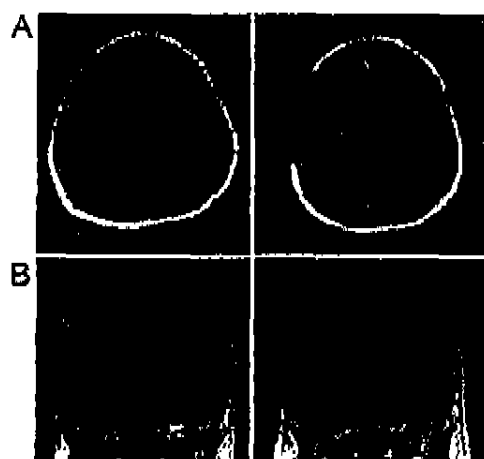


Fig. 5. Exemplary T1-weighted, post contrast, MRI scans of recurrent GBM patients before (Left) and after (Right) TTFields treatment. (A) Complete response after 8 months of treatment. (B) Stable disease (10% reduction in contrast enhancing area) after 9 months of treatment.

Discussion

Alternating electric fields have been shown to have a wide range of effects on living tissues. At very low frequencies (<1 KHz), electric fields stimulate excitable tissues through membrane depolarization (13) and have been claimed to stimulate bone growth and accelerate fracture healing (14). However, as the frequency of the electric field increases the stimulatory effect diminishes, whereas above MHz a completely different biological effect, tissue heating, becomes dominant (15, 16).

Alternating electric fields of intermediate frequencies (10 kHz to 1 MHz) were considered not to have any meaningful non-thermal biological effects (5). An exception, are the TTFields described in ref. 9. This presumed lack of effect of such fields is consistent with the fact that when electric fields, that exert forces only on charges and dipoles reverse direction at a high frequency, their net effect tends to null out. Thus, the effects were minor and have neither been shown to be beneficial or detrimental to humans (5, 8, 17).

In this study we try to use TTFields as a new cancer treatment modality. We first extended the *In-Vitro* study of TTFields effect on glioma and melanoma cells (9) to several of the most prevalent cancers: breast carcinoma and non-small-cell lung carcinoma. It was found that the proliferation of these cells is arrested and the cells are destroyed (Fig. 2). The optimal frequencies differed between cancer cell types. To understand this finding we calculated the force on a 1 μ m polarizable spherical particle in a dividing cell as function of cell radius, membrane thickness and cytoplasm conductivity. It was found that optimal TTFields frequency is inversely related to cell size (see S1 Appendix A) in a way consistent the diameter variability of the different cell types studied.

In the previous study (9) animal treatment was done by using implanted electrodes. In the present study, we used the much more practical externally applied electrodes. Furthermore, as the available data suggests that treatment may need to be prolonged, the use of conducting electrodes may result in serious problems: local damage to the skin because of electrolysis and the generation of free radicals at the electrode-tissue interface, skin permeabilization by the transdermal currents (18, 19), and calcium accumulation within cells (20) that can result in cell death (21). Clearly, the first 2 adverse effects do not occur at the surface of insulated electrodes. Using fluorescence calcium imaging techniques, we could demonstrate that electric field

induced calcium accumulation is eliminated by the use of insulated electrodes (see S1 Appendix B). However, the large potential drop across the insulation high impedance poses a serious problem; to generate the fields of the required intensity potentials of $>1,000$ V must be used. As such high voltages may compromise patient safety, low impedance electrodes were developed. The impedance of insulation is lowered by using an insulating material, lead magnesium niobate-lead titanate (PMN-PT) (EDO, New York, NY), that has a dielectric constant of $\epsilon > 5,000$. Under these conditions the electrodes have a capacitance of ~ 10 nF/cm², i.e., an impedance of 100–200 Ω at the TTFields frequency range. Thus, only 50% of the applied voltage is lost on the insulation in the mice experiments. The corresponding potential drop on the 22.5 cm² electrodes placed on the patient's head, in the trial presented here, is only $\sim 10\%$ of the applied voltage.

A major limitation of all current cancer treatments is their unfavorable therapeutic index. Two types of toxicities may be expected from an electric field based treatment. First, the fields could theoretically affect excitable tissues causing cardiac arrhythmias or seizures. However, such effects are not expected to occur, because for sinusoidal alternating fields of >10 KHz, excitation of nerves and muscles decreases dramatically, because of the parallel resistor-capacitor nature of the cell membrane (22). Indeed, in both acute and chronic application of TTFields to animals and patients, there was no trace of abnormal cardiac or neurological activity. Secondly, TTFields might be expected to damage rapidly dividing normal cells within the body, i.e., bone marrow and small intestine mucosa. However, no treatment-related toxicities were found in any of the treated patients or upon animal exposure to field intensities threefold higher than the effective anti-tumoral dose. With regards to hematopoiesis the reason for this is that these cells, which reside mainly in the bone marrow, are protected from the TTFields by the high impedance of both the bone and bone marrow (23). This was demonstrated by calculating the TTFields distribution in an extremity, such as a leg, by using the finite element mesh (FEM) method. It was found that the field intensity is 100-fold lower within the bone marrow compared with the surrounding tissues. The lack of damage to intestinal mucosa probably reflects that the small intestine mucosal cells have a slower replication cycle than neoplastic cells (24) and that the intestine changes its orientation, relative to the applied field, often lowering the efficacy of the mitotic disruption.

The tumor inhibitory effect of TTFields has been attributed previously to two separate mechanisms (9): interference with the formation of the mitotic spindle microtubules and physical destruction of cells during cleavage, both of which are strongly dependant on the orientation of mitosis axis versus the field vectors. Because the relative orientation of the mitosis axis during cytokinesis is random, it would be expected that only a fraction of dividing cells would be affected by TTFields of any specific direction. To overcome this problem, we applied sequentially several field directions and have shown that increasing the number of directions from 1 to 3, resulted in a significant increase in the anti-proliferative efficacy of TTFields *in vitro* and *in vivo*.

Following encouraging evidence from experimental animals, a clinical trial of the effect of TTFields on patients with recurrent GBM was initiated. Because *in vitro* data indicate that TTFields are most effective when applied for >16 h continuously (data not shown), patients were treated daily for an average of 18 h per day until progression. The results reported here are the first evidence of the safety and efficacy of TTFields used to treat cancer in patients. Preliminary accounts of this data were published in

abstract form.¹¹³⁸⁷⁹ Because this was a pilot trial there was no randomized control group and the results were evaluated by comparing to historical control data. Most historically controlled pilot studies in recurrent GBM are compared with a large metaanalysis performed by Wong *et al.* In 1999 (10) and to this data we added the four prospective trials (25–28), which included >50 GBM patients, performed since that date. The average historical PFS6 based on the above studies is $15.3 \pm 3.8\%$, and the average historical TTP is 9.5 ± 1.6 weeks. OS averaged 29.3 ± 6 weeks (see SI Table 2). When compared with these outcomes, the efficacy data collected in the current pilot trial is extremely promising (TTP, 26.1 weeks; PFS6, 50%; and OS, 62.2 weeks). These results were not accompanied by hematological or gastrointestinal toxicities, epileptic seizures, cardiac arrhythmias, etc., despite >70 months of cumulative treatment. The only side effect detected was contact dermatitis beneath the electrodes. This reaction is most likely the result of a combination of factors, including chronic moisture, heat, and occlusion of the skin; chemical irritation by constituents of the hydrogel and medical tape (29); and possibly inhibition of cellular replication in the skin by the TTFields. Thus, in conclusion, this treatment modality was well tolerated and caused almost no toxicity at all.

In summary, we demonstrated initially that TTFields are effective in arresting the proliferation and inducing death in a wide range of tumor cells in culture as well as solid tumors in animals. On this basis a clinical trial was carried out treating human patients suffering from recurrent GBM, a malignant brain tumor. It was demonstrated that the TTFields inhibit the growth of this highly treatment-resistant tumor by using special insulated electrodes, with little or no side effects. Can we expect to have similar efficacy on other human tumors? The fact that in cultures and animal models TTFields were found to be effective on all cells and tumors tested is definitely encouraging. Furthermore, TTFields being a physical, rather than chemical, modality, their efficacy is likely to be highly insensitive to specific interactions with tumor and patient receptors and other characteristic elements. Thus, like irradiation, they have the potential to be effective over a wide range of tumors. However, from the above it is apparent that their practical specificity to cancerous cells is significantly higher than that of irradiation, the therapeutic efficacy of which is often severely limited by toxicity. Therefore, we believe that there is a high probability that TTFields may prove to be an effective and safe therapeutic modality to a large number of human cancers.

Materials and Methods

Cell Cultures. Cell cultures were grown in DMEM plus 10% FCS media in a CO₂ incubator (5% CO₂) at 37°C. Cell suspension (200 μ l total 20×10^4 cells) were placed as a drop in the centre of 35-mm Petri dishes, incubated for 24 h and then the cell number was estimated by using standard XTT method (Cell proliferation assay Kit, Biological Industries Ltd., Israel) and expressed as OD₄. Temperature was measured by a thermocouple (Omega, Stamford, CT) placed at the center of the dish. Two pairs of electrodes, insulated by a high dielectric constant ceramic [lead magnesium niobate–lead titanate (PMN-PT)], positioned in the petri dish perpendicular to each other were connected to a sinusoidal function generator and amplifier. Two-directional fields were generated sequentially (1) by switching the output of the amplifier between two pairs of electrodes every

0.25–1 sec. The electric field intensity in the culture medium was measured as described in ref. 1.

At the end of 24 h of treatment, the cell number was measured by using the XTT method and expressed as OD₄. The rate of cell proliferation was expressed as the OD₄/OD₀ ratio.

Animal Models. Tumor inoculation and in vivo size assessment. Animal experiments were conducted after approval by the Technion-Israel Institute of Technology committee for the care of laboratory animals. Intracranial glioma (F-98) was inoculated stereotactically into the subcortical white matter in the right hemisphere of Fischer rats (Harlan laboratories, Israel) by using a modification of the method described in refs. 30 and 31. Briefly, a hole, 1 mm in diameter, was punched through the scalp, 2 mm to the right of the midline and 4 mm rostral to the line connecting the external ear canals. A 0.5 mm burr hole was drilled in the bone at same location and a 26G needle was inserted to a depth of 7 mm beneath the scalp surface. Five microliters of saline containing 2.5×10^5 F-98 cells was then injected by using a microsyringe operated by a micromanipulator. The needle was left in position for 60 sec and then retracted slowly at a rate of 2 mm/min. Rats were allowed to recuperate for 24 h before treatment initiation. Tumor volume was assessed based on serial (2-mm interval) T1 weighted axial MRI images (0.5 Tesla MRI; Gyrex orbital coil; Elscint, Haifa, Israel) obtained 10 min following injection of 0.7 ml of Gadolinium (Magnetol; Soreq Radiopharmaceuticals, Yavne, Israel) into the tail vein. Tumor volume was assessed by calculating the area in square millimeters of the contrast enhanced lesion in each section. In view of the small size of the head of the rat, only three electrodes could be positioned on it, generating one to three different field directions.

Computation of the distribution of electric fields generated by external insulated electrodes. The distributions of the alternating electric field generated by external electrodes within the brains of rats were estimated by using FEM simulations. These field distributions are determined by the geometry and electrical properties of the electrodes and tissues. On average, the capacitance of each electrode is 8 nF. This translates into an impedance of 190 and 95 Ω at 100 and 200 kHz, respectively. Because the impedance of the rat head is on the order of 400 Ω , when applying 42 V, 200 kHz TTFields to rats, 14-V drop on the insulation of both electrodes and the remaining 28 V on the rat itself. The fields generated in the areas of interest are in the range of 1–2 V/cm. The calculated field distribution for the rat head is given in Fig. 3A.

Human GBM Trial. GBM patient eligibility and characteristics. Twelve patients, suffering from the brain tumor GBM were enrolled to the study. Patients eligible for enrollment had recurrence based on Macdonald criteria (32), were >18 years old, had histologically established GBM (World Health Organization grade IV), had a Karnofsky performance scale ≥ 70 , and were at least 4 weeks from any brain surgery and at least 8 weeks from radiotherapy. Patients could be at any recurrence and may have received other salvage therapies before enrollment. All patients had received adjuvant Temozolomide for their primary tumor. No concomitant chemotherapy was allowed. Multifocal disease was allowed. Patients with significant comorbidities, intracranial tumors, implanted pacemakers or documented clinically significant arrhythmias, were excluded from the trial. During review of the histology from postprogression debulking surgery, one patient was excluded from efficacy analysis because of failure to meet histological criteria for grade IV glioma. An additional patient dropped out of the trial immediately following the baseline visit because of withdrawal of consent. Individual patient characteristics are listed in SI Table 1.

¹¹³⁸⁷⁹Kirson, E. D., Dbaly, V., Nédélec, C., Tavernier, F., Salmers, M., Peiti, V., AACR Meeting Abstracts, April 5, 2006, Washington, DC, Abstract 2539.

¹¹³⁸⁸⁰Dbaly, V., Kirson, E. D., Peiti, Y., Gullin, P. H., Congress of Neurological Surgeons, October 12, 2005, Boston, MA (abstr.).

¹¹³⁸⁸¹Gullin, P., Kirson, E., Peiti, Y., Dbaly, V., International Brain Tumor Research and Therapy Meeting, April 26, 2006, Napa Valley, CA (abstr.).

The clinical trial. A single arm, pilot trial of the safety and efficacy of TTF treatment was performed in 10 patients with recurrent GBM. Written informed consent was obtained from each subject. The trial was performed after approval by the Na Homolce Institutional Review Board and the Czech Ministry of Health. Efficacy analysis was performed for 10 recurrent GBM patients by comparing TTP, PFS6, and OS in recurrent GBM patients treated with the NovoTTF-100A device with the TTP, PFS6, and OS of recurrent GBM patients in a literature based historical control group (10, 25–28). No statistical hypothesis testing was planned because of the small sample size. Ninety-five percent confidence intervals of survival proportions were calculated from Kaplan–Meier survival curves, by using standard formulae (33).

Measurement and simulation of TTF fields intensity within the human brain. To plan the TTF fields intensity necessary to treat patients with intracranial tumors, we performed FEM simulations of the intensity distribution of TTF fields within a three-dimensional model of the human head. Field intensity was slightly higher in the cortex than in the center of the brain (by $\approx 30\%$), but effective (1–2 V/cm) TTF fields could be generated at the center of the brain by applying ≈ 50 V to surface electrodes placed on the scalp. To validate these findings, TTF fields intensity was measured within the brain of a volunteer undergoing surgery because of obstructive hydrocephalus because of a huge meningioma of the pineal region. The study was performed according to an experimental protocol approved by the Ramham Medical Center ethics committee. The measured TTF fields intensity was accurate within 10% of the FEM simulated values.

TTF fields treatment of GBM patients. TTF fields were applied to recurrent GBM patients by using the NovoTTF-100A device (NovoCure Ltd., Haifa, Israel). This portable battery-operated device generates TTF fields in GBM patients by means of insulated electrodes placed on their shaved scalps. The area of each

insulated electrode array used was 22.5 cm^2 . Fields of 1–2 V/cm were generated by controlling the current density through the electrodes $< 31\text{ mA/cm}^2$ RMS, approximately one-third of the level that is generally recognized to present a risk of skin injury (100 mA/cm^2) (34). In addition, the maximal power density beneath the electrodes was kept beneath 0.22 W/cm^2 , i.e., below the level associated with thermal skin injury (35). Electrode temperature was monitored and the power was lowered automatically when the temperature of any electrode exceeded 41°C . This value is well below the threshold of 44°C , i.e., the lowest prolonged temperature that can cause thermal injury (34).

TTF fields having the optimal frequency of 200 kHz for rat and human gliomas (see Fig. 2) and an intensity of 1–2 V/cm (peak) were used in the trial. TTF fields were switched sequentially every 1 sec between two perpendicular directions; lateral and anterior–posterior, through two sets of insulated electrode pairs. Patients received treatment continuously until disease progression or for a maximum of 18 months. Treatment was applied daily for an average of 18 h per day.

Patient evaluation. Objective tumor assessment was performed by Gd-enhanced MRI according to a strictly defined protocol. MRI scanning was performed at trial entry within one week of NovoTTF-100A treatment initiation and after every treatment course (28–30 days). All scans were reviewed by a board certified radiologist (J.V.). The assessment of tumor response was based on criteria defined by MacDonald *et al.* (32). Study visits were performed once per week during the first month of treatment and monthly thereafter. The following examinations were carried out at each visit: Neurological evaluation, EKG, complete blood count with differential, chemistry panel, and coagulation studies. Adverse events occurring during treatment or up to 60 days after termination of therapy were scored according to the common toxicity criteria scale (version 3). Disease progression was not captured as a serious adverse event.

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Disruption of Cancer Cell Replication by Alternating Electric Fields

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ABSTRACT

Low-intensity, intermediate-frequency (100–300 kHz), alternating electric fields, delivered by means of insulated electrodes, were found to have a profound inhibitory effect on the growth rate of a variety of human and rodent tumor cell lines (Patricia C, U-118, U-87, H-1299, MDA231, PC3, B16F1, F-98, C-6, RG2, and CT-26) and malignant tumors in animals. This effect, shown to be nonthermal, selectively affects dividing cells while quiescent cells are left intact. These fields act in two modes: arrest of cell proliferation and destruction of cells while undergoing division. Both effects are demonstrated when such fields are applied for 24 h to cells undergoing mitosis that is oriented roughly along the field direction. The first mode of action is manifested by interference with the proper formation of the mitotic spindle, whereas the second results in rapid disintegration of the dividing cells. Both effects, which are frequency dependent, are consistent with the computed directional forces exerted by these specific fields on charges and dipoles within the dividing cells. *In vivo* treatment of tumors in C57BL/6 and BALB/c mice (B16F1 and CT-26 syngeneic tumor models, respectively), resulted in significant slowing of tumor growth and extensive destruction of tumor cells within 3–6 days. These findings demonstrate the potential applicability of the described electric fields as a novel therapeutic modality for malignant tumors.

INTRODUCTION

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarization (1). The transmission of such fields by radiation is insignificant, and therefore they are usually applied directly by contact electrodes, although some applications have also used insulated electrodes. Some well-known examples of such effects include nerve, muscle, and heart stimulation by alternating electric fields (1, 2). In addition, low-frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing (3). However, as the frequency of the electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions, although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper-depolarization cycles are integrated such that the net effect is nullified. At very high frequencies (i.e., above many MHz), although the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as frequency, field intensity, or tissue dissipation factor increases (4). This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radio frequency tumor ablation, which can be applied through insulated electrodes (5). Intermediate-frequency electric

fields (i.e., tens of kilohertz to megahertz) alternate too fast for causing nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields of low to moderate intensities are commonly considered to have no biological effect (4). However, a number of nonthermal effects of minor biological consequence have been reported even at low field intensities. These include microscopic particle alignment (i.e., the pearl chain effect; Ref. 6) and cell rotation (7, 8). With pulsed electric fields of 10^5 V/cm and 100-ns pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation (9).

In the present study we show for the first time, to our knowledge, that very low-intensity (<2 V/cm), intermediate-frequency (100–300 kHz), alternating electric fields induced by insulated electrodes have specific inhibitory effects on dividing cells in culture. We demonstrate that applying these fields to cancerous cells leads to proliferation arrest and cell destruction. When applied to syngeneic mice tumor models, these tumor treating fields (TTFields) cause a significant reduction in tumor growth rate without any significant side effects.

MATERIALS AND METHODS

In Vitro Experimental Set Up. Cultures were grown in standard culture dishes (4-well cell culture chambers; 3N 138 (2); Nalge Nunc International). The TTFields were generated by pairs of 15-mm-long, completely insulated wires (P/N K-30-1000; VT Corporation; outer diameter, 0.5 mm; ethylene tetrafluoroethylene insulation thickness, 0.125 mm; dielectric breakdown, 1800 V/mm) fixed to the bottom of each dish at a distance of 1 mm from each other. The wires were connected to an oscillator (GF8219A; Instek) and a high-voltage amplifier (A303; A. A. Lab Systems Ltd.) that generated the required sine-wave signals (range, 300–800 V). Cells were plated by carefully smearing 10^4 cells along the gap between the wires (Fig. 1A). After the cells settled and attached to the plate surface, 500 μ l of DMEM were added to each culture dish, which was then transferred to a 5% CO₂ humidified incubator held at 36°C. The culture was incubated for a control period of 24 h before treatment. Culture medium was replaced manually every 24 h throughout the experiments. TTFields were then applied by connecting the wires to a high-voltage amplifier operated by a signal generator with frequency and amplitude controls. Finite element simulation of the TTFields generated between the wires demonstrated that the field in the vicinity of the cell culture was homogenous (not shown). Eleven different types of cancerous cell lines were subjected to TTFields. These included human melanoma (Patricia), glioma (U-118, U-87), Lung (H-1299), prostate (PC3), and breast (MDA231) cancerous cell lines as well as mouse melanoma (B16F1), rat glioma (F-98, C-6, and RG2), and mouse adenocarcinoma (CT-26) cell lines (all from American Type Culture Collection, except for Patricia, which was a generous gift from Dr. Ruth Halaban, Department of Dermatology, Yale University School of Medicine). In addition, a noncancerous cell line (BHK) was grown under conditions that stunt cell replication (0.1% FCS) and then subjected to TTFields. Also, segments of excised rat mesentery and diaphragm were subjected to the fields *in vitro*. Colorimetric cell counts were made every 24 h after seeding using the standard 2,3-bis(2-methoxy-4-nitro-5-sulphophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide method to measure cell proliferation as described previously (10) using cell proliferation assay kit (Biological Industries, Beit Haemek, Israel). In brief, culture media was replaced with 0.2 ml of preheated 2,3-bis(2-methoxy-4-nitro-5-sulphophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide reagent and incubated for 1 h at 37°C in a 5% CO₂ incubator. After incubation and gentle stirring,

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0.15 ml of the reaction solution was transferred to a 96-well plate (BN 92696; TPP, Trasandigen, Switzerland). The absorbance of the samples was then read with a spectrophotometer (Tecan ELISA Reader; 450 nm). The colorimetric measurements at each time point were normalized to the measurement performed immediately before beginning of treatment. To verify that the colorimetric assessments were accurate, direct visual cell counts were performed on sample culture dishes. At the optic densities used (0.2–2), optic density was linearly related to the number of cells in the culture dishes ($n = 10$; $r^2 = 0.99$). The growth rate of both treated (GR_t) and control cultures (GR_c) was calculated for each experiment by plotting the optic density values on a logarithmic scale and fitting a linear regression line to the values. The growth rate for each culture dish was the slope of this linear regression. The therapeutic enhancement ratio (TER) was calculated as the ratio of the decrease in the growth rate of treated cells compared with the growth rate of control cells $[(GR_c - GR_t)/GR_c]$. Thus, if the increase in the number of treated cells is equal to that of the controls, $TER = 0$; if the increase in cell number is smaller in the treated cultures than in the controls, $TER > 0$; and if the number of cells in the treated cultures decreases absolutely, $TER > 1$.

In time-lapse microphotography experiments, cell lines were grown on a 35-mm standard culture dish (BN 430165; Corning Inc.) by plating 3×10^4 cells in 2.5 ml of DMEM with 25 mM HEPES. The Petri dish lampcathode was controlled at 34°C (B16F1) or at 37°C (all other cell lines). Subsequently, two parallel insulated wires were positioned on the bottom of the dish with 1 mm distance between them through which TTFields were applied. The entire set-up was placed on an inverted microscope (Eclipse TS-100; Nikon) and video microphotographs at $\times 200$ magnification were taken with a standard VCR camera (Handicam X 320; Sony). Photographs were captured using a personal computer every 60–120 s for 6–10 h/culture.

Fluorescent Labeling of α -Tubulin, Actin, and DNA. Mouse melanoma cells were grown on coverslips and subjected to TTFields for 24 h. After treatment, the medium was removed, and the cells were washed in a buffer solution [10 mM 4-morpholinethanesulfonic acid, 150 mM NaCl, 5 mM EGTA, 5 mM $MgCl_2$, and 5 mM glucose (pH 6.1)], permeabilized, and fixed with 0.5% Triton X-100 and 0.25% glutaraldehyde (Sigma) for 5 min and then post-fixed with 1% glutaraldehyde for 20 min. Subsequently, the cells were washed in PBS and 1 mM sodium borohydride (Sigma) to eliminate autofluorescence. The coverslips were then incubated with a primary antibody clone for α -tubulin (DM1A; Sigma) for 30 min, washed, and incubated for 30 min with a secondary antibody (Alexa Fluor 488 goat anti-mouse IgG; Molecular Probes). Rhodamine-conjugated phalloidin (Sigma) was added with the secondary antibody to stain actin filaments. The cells were then washed and incubated with 4',6-diamidino-2-phenylindole (Molecular Probes) to stain the DNA. After staining, the coverslips were mounted and viewed with a fluorescence microscope at $\times 630$ magnification and photographed.

Electric Field Measurement. The electric field intensity in the culture medium was measured by means of a probe, consisting of two (0.25 mm in diameter) insulated wires with exposed tips 0.5 mm apart, that was dipped in the culture medium. The wires were connected to a high-input impedance differential amplifier that translated the waveform amplitude into a calibrated steady voltage that was digitally recorded. Field intensities throughout the manuscript are expressed in peak voltage amplitude per centimeter (V/cm). Care was taken to eliminate any pickup from the field outside the culture medium. Continuous field monitoring could also be made by measuring the potential drop across a 100 Ω resistor placed in series with one of the field-generating wires. The voltage drop on this resistor was linearly correlated to the field intensity ($r^2 = 0.96$). To verify that the experimental setups were not exposed to any significant magnetic fields, the electromagnetic radiation in the immediate vicinity of the treated cultures was measured using a loop antenna (EMCO 6507 1 kHz to 30 MHz) connected to a spectrum analyzer (Anritsu 9 kHz to 2.2 GHz). The electromagnetic radiation in the 100–300-kHz range within the incubators containing treated culture dishes was found to be 10^{-12} Tesla and within animal cages containing TTField-treated mice, 10^{-14} Tesla, i.e., negligible.

Finite Element Simulations of Electric Field Distribution. The calculations of the electric field within the cells are based on finite element mesh (11), using a simplified description of the cell morphology (see Fig. 7). In all calculations, the dielectric constant of both the cytoplasm and medium was 80, their conductance was 0.3 S/m, the cell diameter was 10 μ m, and the membrane thickness was 3 nm (with a dielectric constant of 3). The electric field

intensity was mapped within the cell, based on the amplitude (1 V/cm), frequency (100 kHz) and waveform (sine) of the electric field applied to the cell culture. The force exerted by an inhomogeneous field, such as that created inside the cells on a single tubulin dimer, was calculated based on the direct interaction between the electric field and the dipole. The force exerted on a microscopically polarizable organelle was calculated by the following equation (12):

$$\langle \vec{F} \rangle = 2\pi r^2 \epsilon_m \text{Re}[K(\omega)] \nabla E_{\text{RMS}}^2 \quad (1)$$

where $\langle \vec{F} \rangle$ is the expectation value of the force vector, Re symbolized the real component of the variable, ∇ is the divergence of the variable, ϵ_m is the cytoplasm dielectric constant, r is the tubulin dimer length or particle radius, E_{RMS} is the RMS value of the electric field, and $K(\omega)$ is the Clausius-Mossotti factor:

$$K(\omega) = \frac{\epsilon_p^* - \epsilon_m^*}{\epsilon_p^* + 2\epsilon_m^*} \quad (2)$$

$$\epsilon^* = \epsilon - i \frac{\sigma}{\omega}$$

where ϵ_p^* , ϵ_m^* are the complex dielectric constants of the particle and cytoplasm respectively, each of which is calculated from the dielectric constant (ϵ) and conductance (σ) as a function of frequency (ω). $K(\omega)$ in this case is always positive at the relatively low frequencies used (i.e., 100 kHz), assuming that at these frequencies, $\epsilon_p^* > \epsilon_m^*$. This means that the force acting on a polarizable particle will always act in the direction of the convergence of the electric field lines. The terminal velocity of particles due to these forces was calculated using Stoke's law.

In Vivo Experimental Setup. TTField treatment was applied by means of 10-mm-long pairs of parallel, insulated wires (outer diameter, 0.5 mm; insulation thickness, 0.125 mm; Tefzel) placed intradermally on the back of a mouse. Another pair of identical wires was placed parallel to the first pair in each mouse, with an interval of 5 mm between the pairs. Cell line inoculums were injected (4 μ l; 3×10^5 cells) intradermally in between the two members of each pair of implanted wires. Only one pair was then connected to a voltage amplifier to apply 100 kHz of TTFields treatment to one tumor. The other pair of wires was left disconnected, and the tumor between them served as a paired control of the treated tumor (see Fig. 1B). Tumors were measured using a caliper. Tumor size was calculated by multiplying maximal tumor length by maximal tumor width. Animal experiments were conducted in accordance with the Technion-Israel Institute of Technology guidelines for the care of laboratory animals.

RESULTS

Effect of TTFields on Cells in Culture. More than 500 culture dishes were exposed to TTFields. The number of cells in each treatment dish was assessed periodically using colorimetric determination (as described in "Materials and Methods"). Because under control conditions, most of the cell lines had doubling times of less than 24 h (range, 17–24 h; except for PC-3 for which the doubling time was 73 h), treatment duration was at least 24 h. Exposure began 24 h after seeding and was continued for up to 72 h. In all cell lines tested, 24-h exposure to TTFields at 100 kHz (at an intensity of 1.0–1.4 V/cm) caused significant inhibition of cell proliferation (TER range, 0.14–0.96; $P < 0.05$; Fig. 1C). This effect lasted beyond the exposure time of the cells to TTFields. In fact in some experiments (e.g., malignant melanoma), culture growth was stunted for as long as 72 h after TTField exposure was terminated (Fig. 2A).

We next checked whether nonreplicating cultures and tissues are affected by TTFields. BHK cultures were maintained in low-serum (0.1% FCS) conditions to slow their replication rate. These cultures were then exposed to 100 kHz of TTFields (at an intensity of 1.2 V/cm) for 24 h. No significant difference in cell number between control and TTField-treated cultures was observed under these con-

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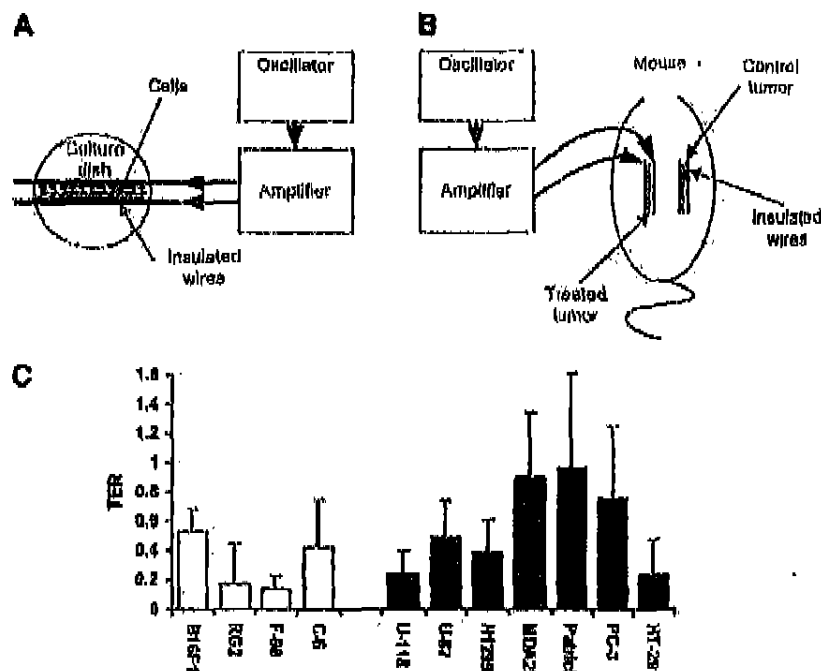


Fig. 1. Schematic representations of experimental setups *in vitro* (A) and *in vivo* (B) are shown. C. TTFIELDS inhibit the growth of cancerous cell lines *in vitro*. Cultures were exposed to 100 kHz TTFIELDS at an intensity of 1-1.4 V/cm. *O*-square, TTER, i.e., the ratio of the decrease in the growth rate of treated cells compared with the growth rate of control cells ($(GR_c - GR_t)/GR_c$). In all four animal cell lines (□) and seven human cell lines (■) tested, the ratio is greater than 0, indicating an inhibition in the growth rate of the treated cultures compared with temperature-matched controls. All effects were statistically significant ($P < 0.05$; Student's *t* test).

ditions ($P = 0.97$). After returning these cultures to normal media (10% FCS), normal replication resumed both in cultures exposed to TTFIELDS and in control cultures. We also tested the effect of TTFIELD treatment on the number of viable cells in nonreplicating tissues dissected from rats. Four segments of rat mesentery and four segments of rat diaphragm were exposed to 100 kHz of TTFIELDS at an intensity of 1.2 V/cm for 24 h. No differences were observed between the number of viable cells in both types of treated tissues compared with control tissues (mesentery, $P = 0.3$; diaphragm, $P = 0.54$).

To test the relationship between TTFIELD intensity and inhibition of cell proliferation, mouse melanoma (B16F1) and rat glioma (F-98) cell lines were exposed to TTFIELDS of different intensities between 1 and 2.5 V/cm. The inhibitory effect of TTFIELDS on cell proliferation increased as intensity was raised (Fig. 2B) until complete proliferation arrest was achieved at intensities of 1.4 and 2.25 V/cm in melanoma and glioma cells, respectively.

The effects of TTFIELDS are expected to be frequency dependent in view of the dependence of cell membrane electric impedance on frequency (due to the cell membrane capacitance). These changes in impedance render the fraction of field penetrating the cells a function of frequency. Therefore, we tested the frequency dependence of the inhibitory effect of TTFIELDS on growth rate of cultured melanoma (B16F1) and glioma (F-98) cells. Comparison between the efficacy of the TTFIELDS at different frequencies was performed by normalizing the TTER to the electric field intensity. As seen in Fig. 2C, the inhibitory effect of TTFIELDS was frequency dependent. Interestingly, the frequency at which maximal inhibition was achieved differed between cell types (120 kHz versus ~200 kHz for melanoma and glioma, respectively).

The Effects of TTFIELDS on Cellular and Molecular Processes in Proliferating Cells. To gain insight into the cellular processes by means of which TTFIELDS affect cell proliferation, time-lapse microphotography was performed while TTFIELDS were applied to mouse melanoma cultures (see "Materials and Methods"). Several unique processes became evident in time-lapse microphotography of TTFIELD-treated cultures. The most pronounced phenomenon was

prolongation of mitosis. In the treated cells, mitosis seemed to begin normally but was prolonged for variable periods of time before completing cleavage into two daughter cells. Fig. 3A shows an exemplary mitosis in a TTFIELDS-treated cell. As seen in the treated cell, mitosis was not complete within 3 h. Due to this proliferation arrest, in treated cultures, mitosis lasted on average 124 ± 91 min (mean \pm SD, $n = 53$; range, 40–541 min), whereas under control conditions, average mitosis duration was 62 ± 8 min from cell rounding to cytokinesis (mean \pm SD, $n = 12$; range, 47–78 min). This prolongation is statistically significant ($P < 0.01$, Mann-Whitney *U* test).

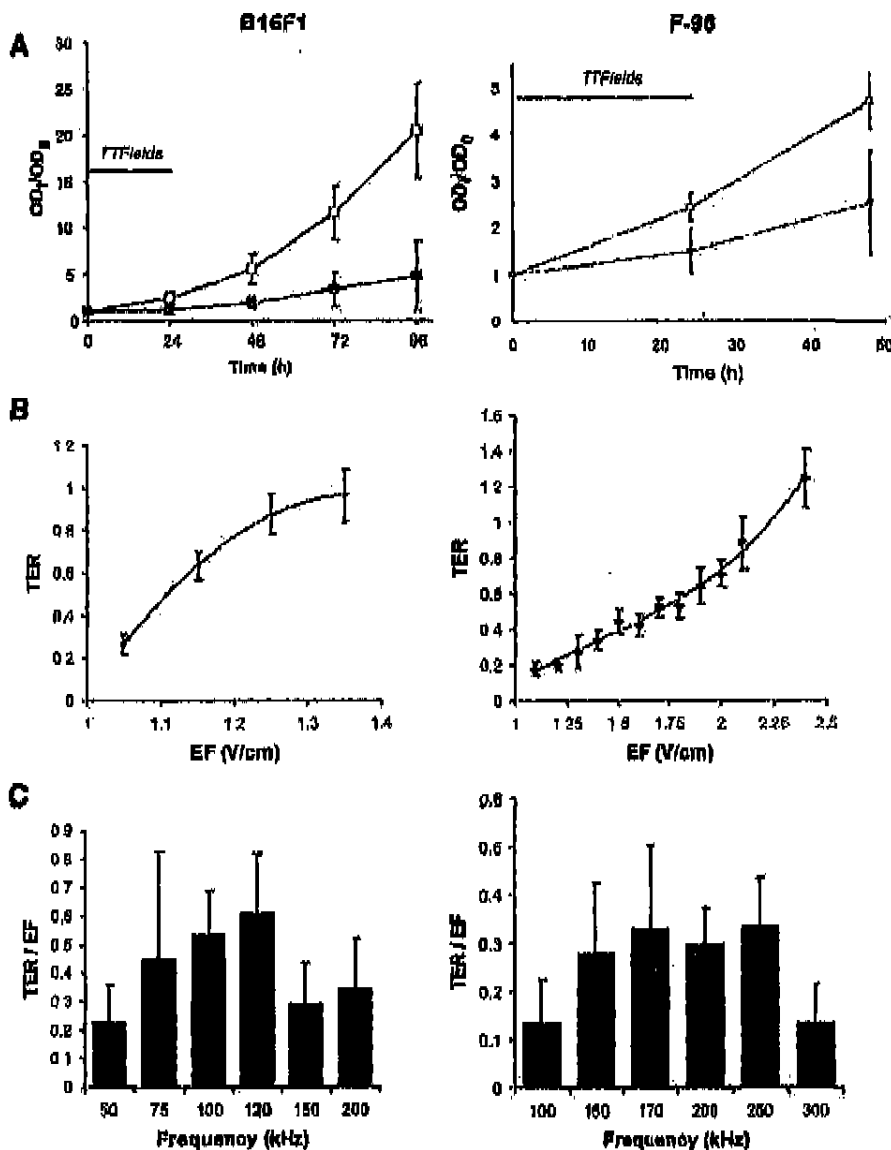
The second major phenomenon, seen in the TTFIELD-treated melanoma cultures, was that one-fourth of cells undergoing mitosis were destroyed as the formation of the cleavage furrow approached complete cell separation. During this process, the cell membrane ruptured, and many small membrane blebs formed, resembling post-mitotic apoptotic cell death (13). Two exemplary cells undergoing such destruction are shown in Fig. 3, B and C. Destructive effects were observed only in mitotic cells, whereas quiescent cells remained morphologically and functionally intact.

The third phenomenon, seen only in TTFIELD-treated cultures, was nuclear rotation. In early mitosis, after cell rounding, nuclei could be seen rotating within the cell. A full rotation lasted on average 15 min. This effect resembles the whole-cell rotation previously described during exposure to intermediate-frequency alternating electric fields (7, 8).

A fundamental characteristic of electric fields is that at any point in space, they have a defined orientation corresponding to the direction of the force they exert on charges and polar elements. With regard to the latter, the force exerted by the field is maximal when the dipole is oriented in the direction of the field. With regard to the above, there are two main structural differences between quiescent and dividing cells. One is that the latter contain highly polar, spatially oriented microtubules and that they develop a directional, hourglass-shaped cell morphology during the cytokinesis phase. In view of these facts, one may expect that the electric field forces will have maximal effect

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Fig. 2. Time, field frequency, and intensity dependence of the effect of TTFields on malignant melanoma (B16F1, left column) and glioma cell (F-98, right column) proliferation. A, the number of cells in untreated cultures (control; \square) as compared with cultures treated with TTFields (\blacksquare). The number of cells at each time point (OD_t) was normalized by the number of cells in the culture before initiation of treatment (OD_0). The number of control cells is seen to roughly double every 24 h throughout the experiment. TTFields were applied for 24 h continuously (solid lines) at 100 kHz in the melanoma cultures and at 200 kHz in the glioma cultures. The increase in the number of treated melanoma (left) and glioma (right) cells over time is significantly smaller than control cells ($P < 0.001$). B, the effect of 24-h exposure to TTFields of increasing intensities. The magnitude of the effect is expressed using the TER. The inhibitory effect of the TTFields on proliferation increases with intensity in both cell types. Complete proliferation arrest (TER = 1) is seen at 1.35 and 2.25 V/cm in melanoma and glioma cells, respectively. EF, electric field. C, change in the melanoma (left) and glioma (right) growth rate after 24 h of exposure to TTFields of different frequencies is normalized to the field intensity (TER/EF). A window effect is seen with maximal inhibition by TTFields at 120 kHz in melanoma cells and at ~200 kHz in glioma cells. Data are mean \pm SE.



on the mitotic process when it is oriented along the lines of force of the field. To investigate this point, we fixed melanoma cell cultures and stained them with toluidine blue, immediately after 24 h of TTField treatment, to demonstrate mitoses and to distinguish vital from damaged or dead cells. The live and damaged mitotic cells (at the time of fixation) were grouped according to the orientation of their cleavage axis relative to the electric field direction. The cells were counted separately in each of four equal sectors that form angles of 0°, 45° (two sectors, 45 and 135), and 90° relative to the field direction. As seen in Fig. 4A, the live cells were randomly distributed in all sectors. In contrast, a much higher proportion of the damaged cells had their axis of division oriented along the field: 56% at 0° versus an average of 15% in each of the other orientations. Surprisingly, the number of cells per unit area in the two 45° sectors was found to be one-half that in the 0° sector. This finding may serve as an indication of an additional effect of TTFields: orientation of the cell division in the field direction. The cells in each of the above spatially oriented defined groups were further divided according to stages of mitosis at the time of fixation. At all stages, a higher fraction of damaged cells

had their axis of division oriented along the field. Moreover, 74% of the parallel oriented cells were damaged while being in metaphase (Fig. 4B).

The spatially organized mitotic spindle, which forms in dividing cells, consists of microtubules that have very large electric dipole moments (14) and may therefore be disoriented by the forces of the electric fields (15, 16). Actin filaments are also polar, however, they have no defined spatial orientation within the cells and are therefore not expected to be significantly affected by the fields. This prompted us to test whether TTFields disrupt mitoses by interfering with the normal formation, orientation, and movement of microtubules as compared with actin filaments as follows: Melanoma cell cultures were treated with TTFields for 24 h. After treatment, the cells were fixed, stained with monoclonal antibodies directed against microtubules and actin filaments, as well as for DNA, and thereafter studied with fluorescence microscopy (see "Materials and Methods"). In control cultures, 95% of cells undergoing mitosis exhibited the normal stages of mitosis with intact mitotic spindles. However, in TTField-treated cultures, more than one-half of the mitoses were abnormal.

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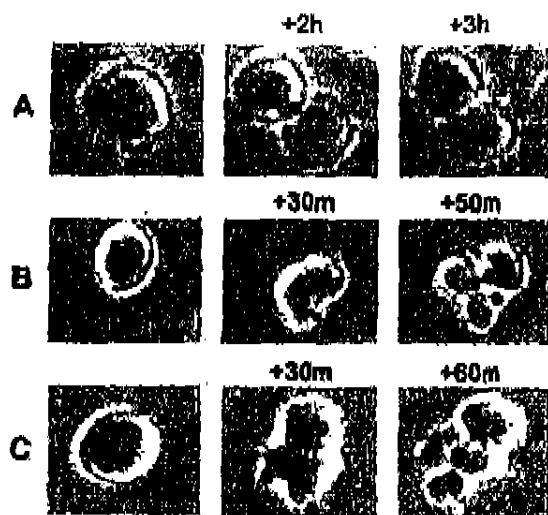


Fig. 3. Time-lapse microphotography of malignant melanoma cells exposed to TTF fields. A, an example of a cell in mitosis treated by TTF fields. Contrary to normal mitosis, the duration of which is less than 1 h, this depleted cell is seen to be multipolar at metaphase for 3 h. B and C, two examples of disintegration of TTF-treated cells during cytokinesis. Three consecutive stages are shown: cell rounding (left), formation of the cleavage furrow (middle), and cell disintegration (right). Scale bar = 10 μ m.

Fig. 5 shows examples of the different forms of abnormal mitosis seen under TTF field treatment. These included polyploid cells in prophase, ill-segregated, multi-spindled and single-spindled cells in metaphase, asymmetric anaphases, and a large proportion of cells in metaphase (>20%) with roseate shaped chromosome assemblies. The normal and abnormal stages of mitosis in control and TTF field-treated cultures are summarized and compared in Fig. 5G. In general, these abnormalities may serve as an indication of interference of TTF fields with the normal behavior of the microtubules. In contrast, staining for actin filaments showed no difference between TTF field-treated and control cultures.

Effect of TTF fields on Tumors *in Vivo*. To test whether TTF fields are effective in destroying tumor cells *in vivo*, we tested their effect on two animal tumor models: C57BL/6 mice inoculated intradermally with malignant melanoma cells (B16F1) and BALB/c mice inoculated intradermally with adenocarcinoma cells (CT-26). TTF fields were generated between implanted (intradermal) wholly insulated wires placed on both sides of the tumor (see Fig. 1B). Mice with implanted electrodes were treated for 3–6 days continuously beginning 1 day after cell line inoculation. We found that 100–200 kHz of TTF fields at low intensities of <2 V/cm effectively inhibited malignant melanoma growth compared with the growth of nontreated control tumors. Photographs of examples of treated and nontreated malignant melanoma tumors are given in Fig. 6 for comparison. Treated tumors were significantly smaller than control tumors at the end of treatment (average treated tumor size was 47% of control tumor size; $n = 78$ mice, $P < 0.001$; Student's t test). Histopathological analysis of treated tumors showed extensive necrosis with aggregations of karyorrhectic and karyolytic debris (Fig. 6F). To test whether TTF fields are effective on different tumor types, BALB/c mice with intradermal adenocarcinomas were treated with the same field parameters. Photographs of examples of such a treated and a nontreated adenocarcinoma tumor are provided for comparison in Fig. 6B. The average effect of TTF fields on adenocarcinoma carrying mice was less dramatic than that seen for malignant melanoma (average treated tumor size was 73% of control tumor size at the end of treatment; $n = 14$ mice). After treatment, the tumors and their adjacent tissues were fixated, stained with H&E, and analyzed histopathologically. No damage to the surrounding tissues was detected.

DISCUSSION

In this study, we have shown that when properly tuned, very low-intensity, intermediate-frequency electric fields (TTF fields) stunt the growth of cancerous cells. We have demonstrated this inhibitory effect in all proliferating cell types tested, whereas, nonproliferating cells and tissues were unaffected. Interestingly, different types of cancerous cells showed specific intensity and frequency dependences of TTF field inhibition. We have demonstrated that two main processes occur at the cellular level during exposure to TTF fields: arrest of proliferation and cell destruction. The damage caused by TTF fields to these replicating cells was shown to be dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is nonnormal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors *in vivo* showed no significant elevation in temperature compared with control cultures/mice. Also, TTF fields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human corneal epithelial cells exposed to constant electric fields (17). At the subcellular level, we have found evidence indicating that TTF fields disrupt the normal polymerization-depolymerization process of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to

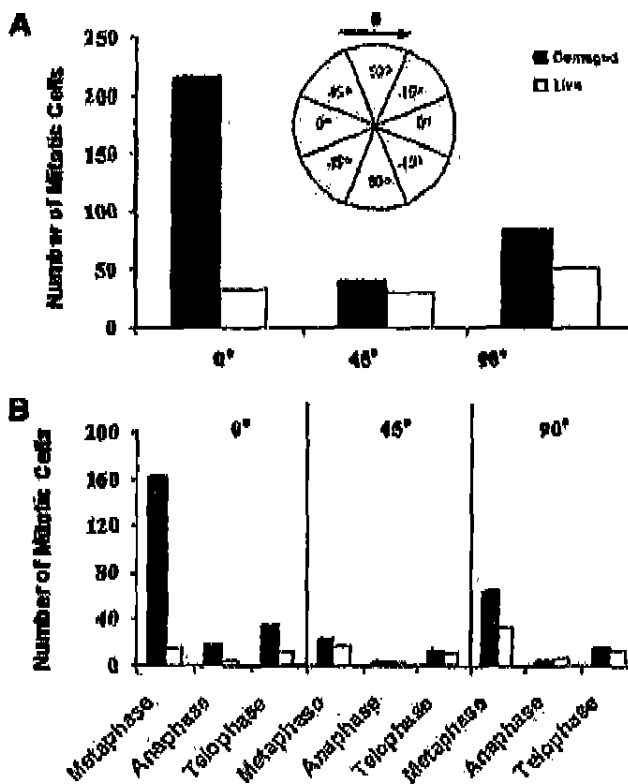


Fig. 4. Dependency of TTF field-induced cellular damage on the orientation of cell division relative to field direction. Ordinate represents the number of mitotic cells counted in their TTF field treated malignant melanoma cultures (100 cells). A, total number of damaged (■) and live (□) mitotic cells in each of three sectors of different applied relative to the field direction (arcs). The number of damaged cells is more than 3-fold larger than the corresponding number of live cells when division is aligned at or close to 0° relative to the electric field direction. In sectors of other angles, the number of damaged cells only slightly exceeds the live ones. Note that because the 45° arc is double that of each of the other two sectors, the number of cells presented in this orientation was halved. B, dividing cell sensitivity to fields of different orientation at different stages of mitosis. When cell division axis is aligned at 0° to the electric field, the number of damaged cells (■) is significantly larger than that of intact cells (□) at all three phases of mitosis. However, the highest number of damaged cells in this orientation is seen at metaphase (8-fold more than intact cells).

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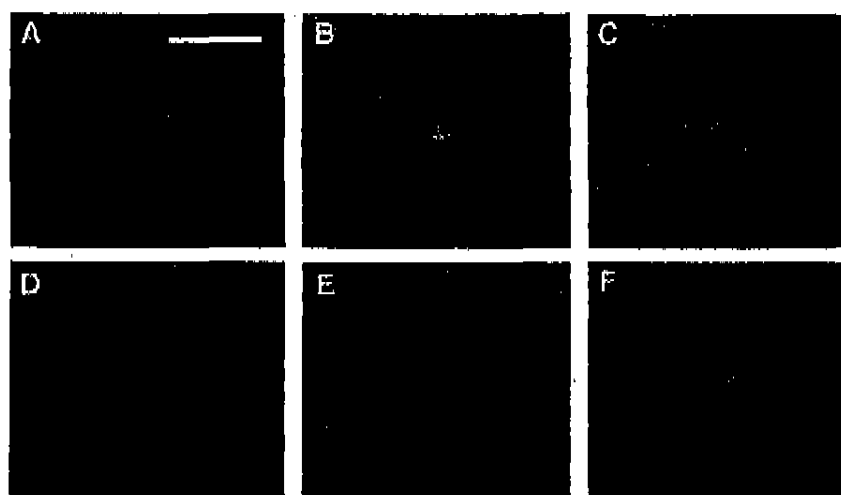
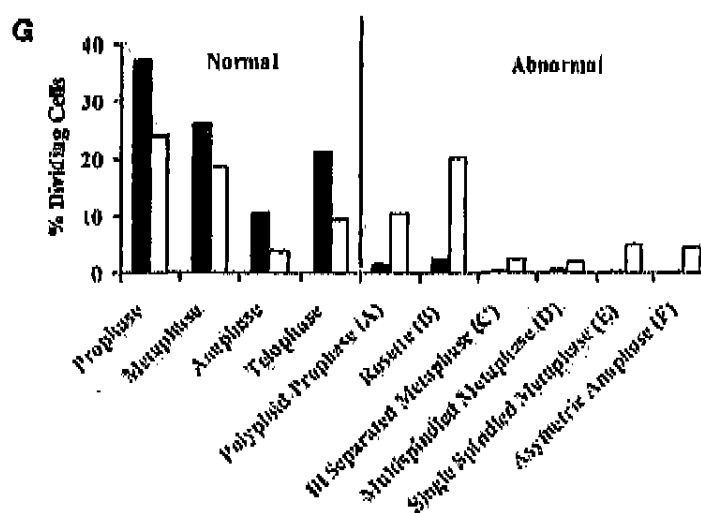


Fig. 5. Immunohistochemical staining of abnormal mitotic figures in TTFIELDS-treated embryos. Malignant melanoma cultures ($n = 4$) were treated for 24 h at 100 kHz and then stained with monoclonal antibodies for microtubules (green), actin (red), and DNA (blue). The photomicrographs show exemplary abnormal mitoses including: polyploid prophase (A); reverse (B); ill-separated metaphase (C); multiploided metaphase (D); single-spindled metaphase (E); and asymmetric anaphase (F). G, the percentage of treated (□) and control (■) mitotic cells in each of the normal and abnormal phases of mitosis.



TTFIELDS are similar to the morphological abnormalities seen in cells treated with agents that interfere directly (18, 19) or indirectly (20–22) with microtubule polymerization (e.g., Taxol).

To explain how TTFIELDS cause orientation-dependent damage to dividing cancerous cells and disrupt the proper formation of the mitotic spindle, we modeled the forces exerted by TTFIELDS on intracellular charges and polar particles using finite element simulations (see "Materials and Methods"). We identified two main mechanisms by means of which the electric fields may affect dividing cells. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14 nm away from the growing end of a microtubule, to orient in the direction of the field (Fig. 7A). This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation (23). This effect can explain the mitotic arrest of TTFIELD-treated cells (24). The second mechanism, which interferes with cell division and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in the simulations depicted in Fig. 7B, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. We see an

increased field line concentration (indicating increased field intensity) at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This inhomogeneity in field intensity exerts a unidirectional electric force on all intracellular charged and polar entities, pulling them toward the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1 μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5 pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization that is 4.3 pN (25). With regard to other particles such as cytoplasmic organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN resulting in their movement toward the furrow at velocities that may approach 0.03 $\mu\text{m/s}$. At such velocity, cytoplasmic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. We also found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTFIELDS on the angle between division axis and the field (Fig. 4). In addition, the calculated dependence of the magnitude of this force on frequency (data not shown) is consistent with the experimentally determined frequency dependence of the

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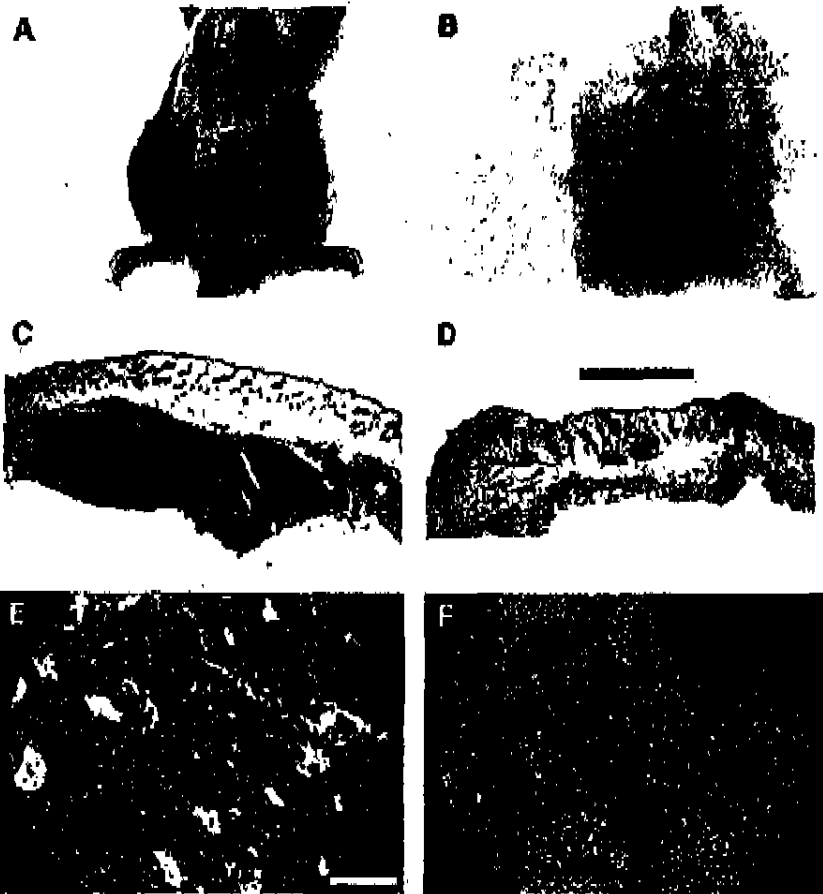


Fig. 6. *In vivo* effects of TTFields on intradermal tumors in mice. Malignant melanoma (A) and adenocarcinoma (B) tumor cells were injected in two parallel locations intradermally on the back of each mouse. Only the tumor on the left side of the mouse was treated. After 4 days of TTFields treatment (at 100 kHz), no tumor can be discerned on the treated side, whereas on the untreated side a large tumor has grown. C-F, histological sections of TTFields-treated intradermal melanoma versus a control (untreated) melanoma on the same mouse. C, after H&E staining, a large (5 mm diameter) nodule of melanoma cells can be seen in the dermis of the control tumor ($\times 40$). Note that due to the large size of the tumor, its deep portion has been lost in preparation. D, treated tumor; only two small (<0.4 mm diameter) nodules are present (scale bar = 0.5 mm). The posttumor structures of the dermis are morphologically intact. E, control tumor; malignant melanoma cells appear intact and viable ($\times 200$). (Scale bar = 100 μ m). F, only necrotic debris and cellular debris are seen in the treated tumor.

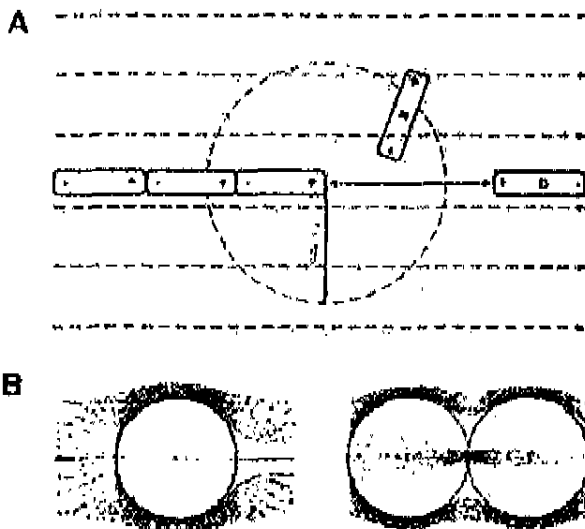


Fig. 7. A, schematic representation of two tubulin dimers positioned near the tip of an elongating microtubule in a dividing cell. The force that a 1-V/cm extracellular TTField exerts on a tubulin dimer located less than 14 nm away from the microtubule tip is smaller than the force exerted by the polar microtubule tip, and therefore it will align according to the field generated by the microtubule. In contrast, dimers further than 14 nm from the end of the microtubule (B) are aligned by the forces of the TTFields (forward flow) in a direction that may not be compatible with the polymerization-depolymerization process. B, finite element mesh simulation of the flux of force of the electric field inside a quiescent cell (left) and a cell undergoing mitotic cytokinesis (right). The diameters of the cells in the simulations was 10 μ m and membrane thickness 3 nm. Inside the quiescent cell, the electric field is mostly uniform (equal distances between the lines of force). In contrast, in the dividing cell, the field is inhomogeneous—the field intensity (line density) increases toward the cleavage furrow.

inhibitory effect of TTFields on melanoma and glioma cell proliferation (Fig. 2C).

In conclusion, we have demonstrated that TTFields inhibit both the proliferation of malignant cells in culture and the growth of tumors in mice while showing no general side effects or local histopathological damage. The mechanism of action of the fields is, at least in part, dependent on disruption of the microtubules of the mitotic spindle and the electric forces resulting from focusing of the field in the dividing cells. The highly specific effects of these fields on dividing cells, together with the relative ease of applying them, focusing them, and screening from them, make them an attractive candidate to serve as a novel treatment modality for cancer.

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RESEARCH ARTICLE

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TTFields alone and in combination with chemotherapeutic agents effectively reduce the viability of MDR cell sub-lines that over-express ABC transporters

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Abstract

Background: Exposure of cancer cells to chemotherapeutic agents may result in reduced sensitivity to structurally unrelated agents, a phenomenon known as multidrug resistance, MDR. The purpose of this study is to investigate cell growth inhibition of wild type and the corresponding MDR cells by Tumor Treating Fields - TTFields, a new cancer treatment modality that is free of systemic toxicity. The TTFields were applied alone and in combination with paclitaxel and doxorubicin.

Methods: Three pairs of wild type/MDR cell lines, having resistivity resulting from over-expression of ABC transporters, were studied: a clonal derivative (C11) of parental Chinese hamster ovary AAB cells and their emetine-resistant sub-line Emt[®]; human breast cancer cells MCF-7 and their mitoxantrone-resistant sub lines MCF-7/Mx and human breast cancer cells MDA-MB-231 and their doxorubicin resistant MDA-MB-231/Dox cells. TTFields were applied for 72 hours with and without the chemotherapeutic agents. The numbers of viable cells in the treated cultures and the untreated control groups were determined using the XTT assay. Student t-test was applied to assess the significance of the differences between results obtained for each of the three cell pairs.

Results: TTFields caused a similar reduction in the number of viable cells of wild type and MDR cells. Treatments by TTFields/drug combinations resulted in a similar increased reduction in cell survival of wild type and MDR cells. TTFields had no effect on intracellular doxorubicin accumulation in both wild type and MDR cells.

Conclusions: The results indicate that TTFields alone and in combination with paclitaxel and doxorubicin effectively reduce the viability of both wild type and MDR cell sub-lines and thus can potentially be used as an effective treatment of drug resistant tumors.

Background

Multidrug resistance (MDR) [1] is encountered when cancer cells are exposed to chemotherapeutic agents for a few replication cycles. It is manifested in reduced sensitivity to both the specific chemotherapy as well as to a number of structurally unrelated agents. This phenomenon obviously poses a serious impediment to successful chemotherapy. Three decades of multidrug resistance research have identified a number of mechanisms by

means of which cancer cells elude the effects of chemotherapeutic agents. The most often encountered MDR is the one resulting from over-expression of ATP-binding cassette transporters such as P-glycoprotein (MDR1), multidrug resistance-associated protein-1 (MRP1), and the breast cancer resistance protein (BCRP) [1-3]. These transporters, that recognize substrates of diverse chemical nature, lower the intracellular concentration of these substrates and are normally involved in detoxification [4,5].

MDR can potentially be overcome by the use of anti-tumor modalities that are not involved in membrane transport, for example, anti-angiogenic agents and physical

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modalities such as radiotherapy, heat and electric fields. Different types of electric fields were reported to inhibit cancer cell proliferation and cause cancer cell destruction, for example: exposure of cancer cells to low amplitude DC currents [6], low intensity, low frequency (50 Hz) AC currents [7] and the intermediate frequency (100-300 kHz) alternating electric fields, termed TFields [8-12].

TFields are a new physical cancer treatment modality that has recently been demonstrated to be highly effective when applied to cell cultures, animal cancer models, as well as patients suffering from locally advanced and/or metastatic solid tumors [8-12]. TFields are alternating electric fields of low intensity (1-3 V/cm) and intermediate frequency (100 - 300 kHz) that are generated by special insulated electrodes applied to the skin surface. These specially tuned fields have no effect on quiescent cells while having an anti-proliferation and destructive effect on mitotic cells. This effect is due to the fact that during cytokinesis, TFields exert forces that move charged or polar macromolecules and organelles towards the narrow neck, separating the newly forming daughter cells [8,9]. They also interfere with the polymerization processes of the microtubule spindle during cell division. Thus, TFields disrupt the cell structure, inhibit cell division and result in cell death. In contrast to most anti-cancer agents, TFields are not associated with any meaningful systemic toxicity [9-12]. Furthermore, it was recently shown that TFields may be used clinically, not only as an anti-proliferation agent, but also as effective adjuvant to currently used chemotherapeutic agents [9].

In view of the above, the target of the present study was to test the possibility of using TFields for treating multi-drug resistant cancerous and non cancerous cell lines, both as a standalone treatment and in combination with chemotherapy.

Methods

Materials

All cell culture media, serum and media supplements were obtained from Biological Industries, Beth Haemek, Israel. All drugs and chemical agents were obtained from Sigma.

Cell lines

The following cell lines and their drug resistant derivatives were used: A clonal derivative (C11) of parental Chinese hamster ovary A48 cells and their emetine-resistant sub-lines *Emt^{R1}* cells having ATP dependent MDR1 type drug resistance [13], a kind gift from Prof. G. Eytan Dept. of Biology, Technion, Haifa, Israel; Human breast cancer wild type MCF-7 cells, obtained from ATCC and their mitoxantrone-resistant sub-lines MCF-7/Mx having ABCG2 transporter [14], a kind gift from Prof. M. Lisco-

vitch, Dept. of Biological Regulation Weizmann Institute of Science, Rehovot, Israel; Human breast cancer wild type MDA-MB-231 cells obtained from ATCC and from which doxorubicin resistant MDA-MB-231/Dox cells were developed in our laboratory using a stepwise increase in drug concentration protocol. This procedure is identical with that developed for these cells in other laboratories [15] for inducing MDR1 type of ABC transporters. The A48/*Emt^{R1}* cell lines were maintained as a monolayer in minimal essential medium containing 5% fetal calf serum, 2 mM glutamine, 100 units/ml penicillin G, and 100 µg/ml streptomycin sulphate. The *Emt^{R1}* cell medium also included 1 µM of emetine. The MCF-7/MCF-7MX and MDA-MB-231/MDA-MB-231Dox cell lines were maintained under monolayer conditions in DMEM containing 10% fetal calf serum, 2 mM glutamine, 100 units/ml penicillin G, and 100 µg/ml streptomycin sulphate. The MCF-7/Mx cell medium also included 250 nM of mitoxantrone and the MDA-MB-231/Dox cells medium also included 0.1 µM of doxorubicin.

All cells were kept in a 5% CO₂ incubator at 37°C. Exponentially growing cells were passaged twice a week using a standard trypsinization procedure.

Cytotoxicity assay

The level of resistance to doxorubicin and paclitaxel was determined by means of the XTT assay as previously described [8,9]. Briefly, 2×10^4 cells/well were plated in 24-well plate (NUNC), incubated without drugs for 24 h and then the initial number of cells, OD₀, was determined following incubation of with the XTT reagent using ELISA Reader (TECAN Sunrise, USA). The medium was then exchanged with ones containing different drug concentrations, 4 wells for each drug concentration (doxorubicin: 0.001-100 µM; paclitaxel: 0.0001-100 µM). After 72 h, the culture media was discharged, XTT reagent was added and the final cell number, OD_{72 h}, was determined. Data obtained from 3 - 5 experiments were collected and the mean values and standard deviations (SEM) of OD_{72 h}, representing final number of viable cells, were calculated for each drug concentration. Cell survival was presented as percentage of viable cells as compared to the corresponding viable cell number in no - drug controls. Drug concentrations inhibiting cell growth by 50% (IC₅₀) were calculated from relative survival curves using the median-effect principle [16].

Exposure to TFields

As previously described [9,11], two pairs of electrodes, insulated by a ceramic having a very high dielectric constant (NovoCure Ltd, Haifa, Israel), were positioned at 90° with respect to each other in both treatment and control Petri dishes. The distance between the electrodes in each

pair was 20 mm. Each pair of electrodes was alternatively connected for 250 ms to a sinusoidal waveform generator (NovoTTF, NovoCure Ltd. Haifa, Israel) that produced 1.75 V/cm, 150 kHz fields in the medium [8]. The 150 kHz frequency of TTFields was found to be effective for treatment of all cells studied.

Four different sets of conditions in each experiment were conducted for each cell line in conjunction with each chemotherapeutic agent: untreated control cells, cells treated by the chemotherapeutic agent alone, cells exposed to TTFields, and cells having a combined TTFields - Chemo exposure (8 Petri dishes for each condition). After 72 h, the culture media was discharged, XTT reagent was added and the final number of viable cells, OD_{72h} , was determined. Data obtained from 3 - 5 experiments were collected and the mean values and standard deviations (SEM) of OD_{72h} representing final viable cell numbers were calculated for each set of conditions. Cell survival was presented as percentage of viable cells out of the corresponding viable cell number in untreated controls. Student t-test was applied to assess the significance of the differences between results obtained for each of the four conditions tested. In order to assess the extent of possible chemotherapeutic dose reduction when applied in combination with TTFields, dose reduction indexes (DRI) for each TTFields/drug combination were calculated according to [17].

The DRI for the same level of effect (DRI_m) was calculated as the ratio of the concentration of drug alone to that of the combined drug-TTFields treatment:

$DRI_m = D_{m(\text{drug alone})}/D_{m(\text{combined treatment})}$. The DRIs determine the magnitude of dose reduction allowed for each drug when given in combination with TTFields, as compared with the agent dose that achieves the same level of effect. DRI values larger than 1 indicate increased sensitivity to the drug.

Intracellular Doxorubicin Accumulation

The intracellular accumulation of doxorubicin was determined for both wild type and drug resistant sub-lines. Cells were grown in total 16 Petri dishes (35 mm, NUNC) as monolayers for 24 h in drug-free medium and then incubated for 1 h in the absence or presence of doxorubicin with or without exposure to TTFields (1.75 V/cm, 150 kHz) (4 Petri dishes for each treatment condition). The cells were washed with ice cold PBS three times and solubilised with 100 μ l of 2% SDS. The solutions were then transferred to black 96-well plates (NUNC) and doxorubicin fluorescence was measured by spectrofluorometry (ELISA Reader TECAN F-200) at λ_{em} 600 nm and λ_{ex} 450 nm. Data obtained from 2 - 4 experiments were collected and the mean values and standard deviations (SEM) of doxorubicin fluorescence were calculated for each condi-

tion. Student t-test was applied to assess the significance of the differences between results obtained for each of the three cell pairs.

Results

Effect of TTFields on wild type cells and their MDR sub-lines
In order to study the TTFields effect, field intensities that reduce the WT cell survival by about 50% were used. A comparison between the survival of wild type and MDR cells, when exposed to such TTFields, is given in Figure 1. The reduction in the number of viable cells is seen to be very similar (48-61% of control) in all wild type and paired MDR lines. In other words, the drug resistant cell lines have about the same sensitivity to TTFields as their corresponding wild type cell lines.

Exposure to doxorubicin or paclitaxel in combination with TTFields

Figure 2 compares between the cytotoxicity-dose curves of chemotherapeutic agents (paclitaxel and doxorubicin) of wild type cells and MDR sub-lines. It is seen that the resistivity of the MDR sub-lines is manifested in a significant right shift of the drug cytotoxicity-dose curves. As a result of these shifts the calculated IC_{50} values (Table 1) for doxorubicin and paclitaxel, for all pairs of WT-MDR cell lines studied, give very high IC_{50} ratios (resistance index RI): 55 - 79 for doxorubicin and 128 - 653 for paclitaxel.

A comparison between cell viability following separate and combined TTFields/drug exposures are presented in Figure 3. It is seen that in all combined exposures cell survival is lower as compared with exposure to any of the

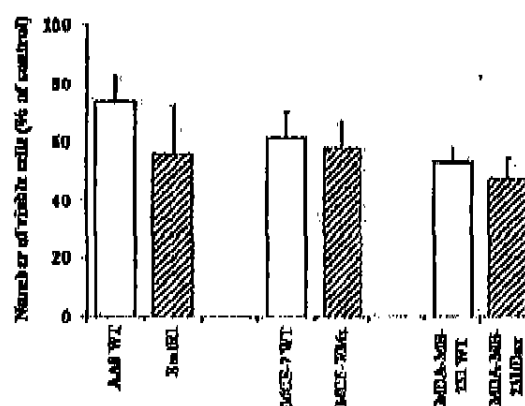
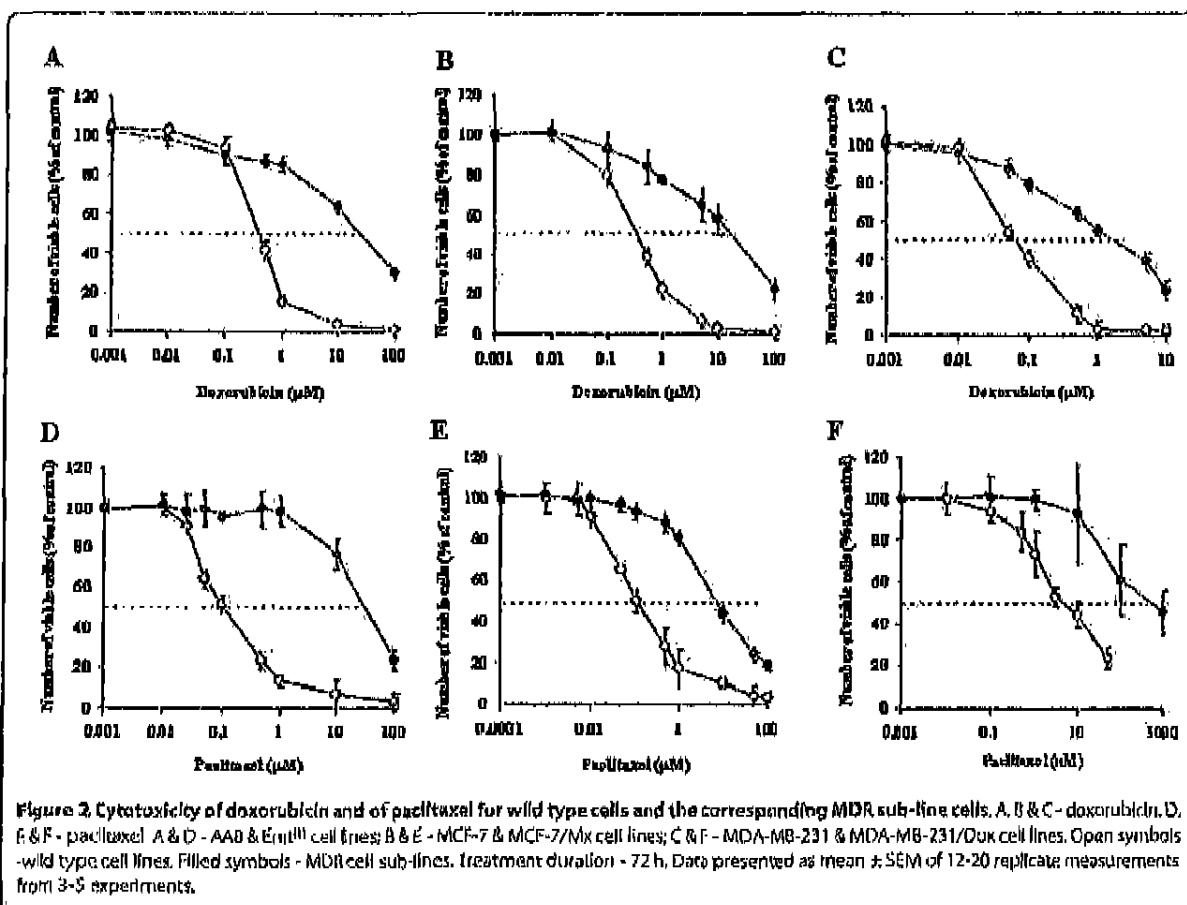


Figure 1 The reduction in the number of viable WT and MDR cells following a 72 h exposure to TTFields. Open bars - WT cells; filled bars - MDR cell sub-lines. TTFields intensity - 1.75 V/cm. Data presented as mean \pm SEM of 30-36 replicate measurements from 4-5 experiments. Note that there is no statistical difference between WT and MDR pairs (student t-test).



chemical agents (doxorubicin or paclitaxel) or TTFields alone (see Figure 1). Moreover, the cell survival of the MDR sub-lines and WT cell lines, when subjected to the combined exposure is similar, i.e. the resistivity or reduced drug sensitivity of MDR cells are not evident under these conditions.

Table 2 summarizes the combined treatment efficacy for MDR cells (see Figures 2 & 3) expressed in terms of Dose Reduction Index (DRI). TTFields are seen to increase the sensitivity to doxorubicin of all three MDR sub-lines by at least two orders of magnitude. The corre-

sponding increase for paclitaxel is even greater, i.e. two to three orders of magnitude. In other words, the efficacy of combined drug/TTFields treatment of MDR cells greatly exceeds that of treatment with drug alone.

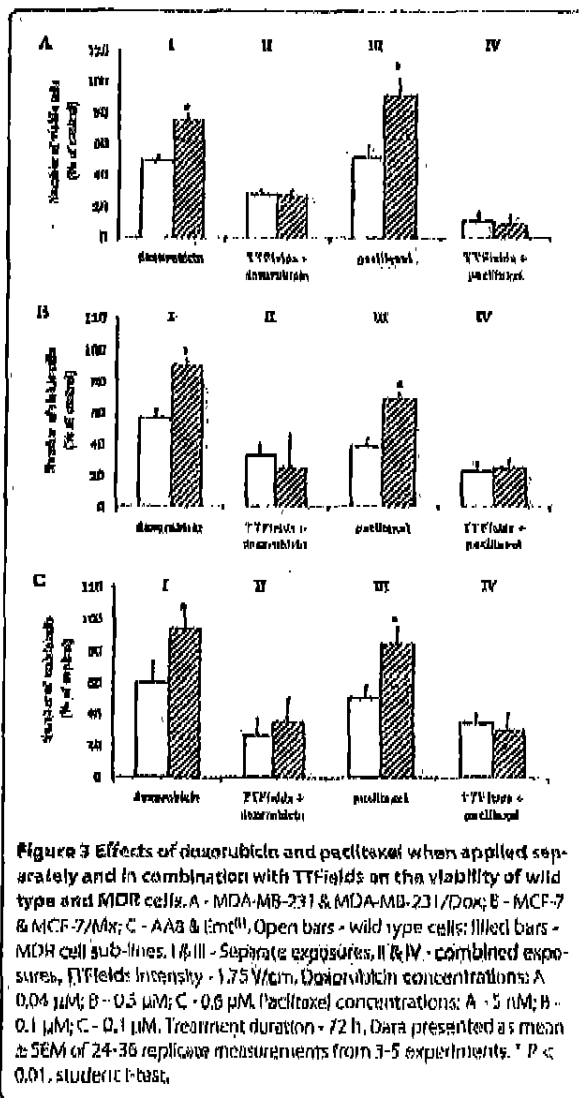
Intracellular Doxorubicin Accumulation

An inherent feature of overexpressed ABC transporters phenotype is the reduction in cell uptake of doxorubicin due to its exclusion [18]. The ability of MDR cells to exclude doxorubicin was determined by means of spectrofluorometric analysis. Figure 4A illustrates the intrac-

Table 1: IC₅₀ values for doxorubicin and paclitaxel

Drug	IC ₅₀					
	A487	EMT6	MCF-7	MCF-7/Mx	MDA-MB-231	MDA-MB-231/Dox
Doxorubicin (μM)	0.6	48.4	0.5	30.5	0.04	2.2
Paclitaxel (μM)	0.1	65.3	0.09	9.9	0.005	0.829

Drug concentrations inhibiting cell growth by 50% (IC₅₀) were calculated from relative survival curves (see Figure 2) using the median-effect principle [16].



cellular concentration of doxorubicin in AA8 (WT) and Emt^{R1} (MDR) cell lines as a function of extracellular doxorubicin concentration with and without exposure to TTFields. As the drug is partially excluded from drug resistant sub line, the relative intracellular doxorubicin concentration in Emt^{R1} cells is lower by 44.9, 49.7 and 49.8% at 15, 30 and 45 μ M extracellular doxorubicin concentration respectively, as compared with the wild type cells (Figure 4A, open symbols). Exposure of AA8 (WT) and Emt^{R1} (MDR) cell lines to TTFields during incubation with doxorubicin had no effect on the intracellular concentration of the drug in both wild type and drug resistant sub lines indicating that TTFields affect neither doxorubicin uptake nor its exclusion (Figure 4A, filled symbols). Figure 4B depicts doxorubicin accumulation by MDR sub lines relative to the corresponding WT cell

Table 2: Dose reduction indexes for MDR cell sub-lines treated alone and in combination with TTFields.

Drug	Dose reduction index (DRI)		
	Emt ^{R1}	MCF-7/Mx	MDA-MB-231/Dox
Doxorubicin	105	195	250
Paclitaxel	815	4404	> 10,000

The DRI estimates the extent to which the dose of one or more agents in the combination can be reduced to achieve effect levels that are comparable with those achieved with single agents. The effect of TTFields/drug combined treatment for each MDR cell sub-line was as shown in Figure 3. The same effect of single drug was obtained from dose-response curves (see Figure 2). The DRI was calculated as a ratio of drug concentrations used alone vs. drug concentrations used in combination with TTFields.

lines exposed to 30 μ M of doxorubicin with and without TTFields. The relative intracellular doxorubicin concentration is lower by $49.7 \pm 5\%$ for Emt^{R1}, $66.4 \pm 5\%$ for MCF-7/Mx and by $32.6 \pm 5\%$ for MDA-MB-231/Dox as compared with the corresponding wild type cells (Figure 4B, open bars). TTFields have no effect on intracellular doxorubicin concentrations in all wild type and drug resistant cell lines (Figure 4B, filled bars).

Discussion

ABC transporters provide vital protection from foreign compounds by exporting these compounds from the cell, thus lowering their intracellular concentration. Unfortunately, exposure of cancer cells to chemotherapeutics, mainly during relapse treatment, causes transporter upregulation such that the resulting over-expression of ABC transporters becomes one of the main causes of treatment failure. Moreover, various tumors such as renal cell, adrenocortical, colon and hepatocellular cancers express ABCB1 and are practically chemoresistant [19]. To overcome this problem chemosensitizers that block ABC transporter-mediated efflux were developed and have been used to combat MDR. However, this approach has not been clinically successful and therefore novel approaches that bypass, rather than block ABC transporters, are being sought for [20]. As the TTFields do not affect drug transport (see Figure 4) they fall into this category.

The results of this study clearly indicate that both the MDR and WT cells are similarly sensitive to TTFields. Moreover, TTFields were shown to enhance MDR cell sensitivity to chemotherapeutic agents, so as to equal that of WT cells under the same set of conditions (Figure 3). This phenomenon can only be partially explained on the basis of the corresponding dose-response curves (Figure 2) and the drug export rate (Figure 4). As demonstrated

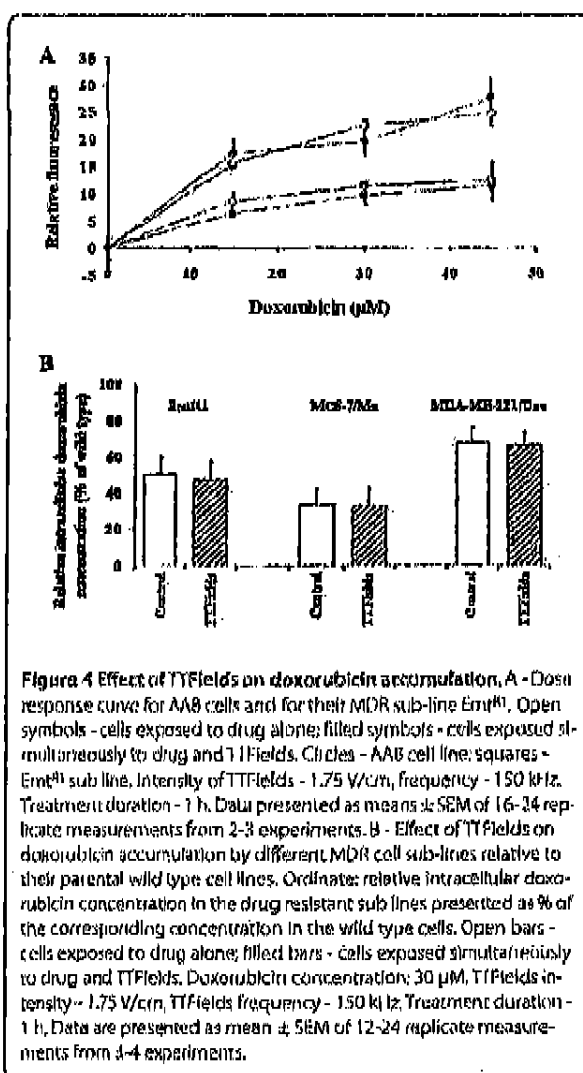


Figure 4 Effect of TTFields on doxorubicin accumulation. **A** - Dose response curve for A46 cells and for their MDR sub-line EmrR. Open symbols - cells exposed to drug alone; filled symbols - cells exposed simultaneously to drug and TTFields. Circles - A46 cell line; squares - EmrR sub-line. Intensity of TTFields - 1.75 V/cm, frequency - 150 kHz. Treatment duration - 1 h. Data presented as means \pm SEM of 16-24 replicate measurements from 2-3 experiments. **B** - Effect of TTFields on doxorubicin accumulation by different MDR cell sub-lines relative to their parental wild type cell lines. Ordinate: relative intracellular doxorubicin concentration in the drug resistant sub-lines presented as % of the corresponding concentration in the wild type cells. Open bars - cells exposed to drug alone; filled bars - cells exposed simultaneously to drug and TTFields. Doxorubicin concentration: 30 μ M. TTFields intensity - 1.75 V/cm, TTFields frequency - 150 kHz. Treatment duration - 1 h. Data are presented as mean \pm SEM of 12-24 replicate measurements from 3-4 experiments.

In Figure 5, the dose-response curve of the drug resistant cells is shifted to the right relative to the WT cells (see also Figure 2). The magnitude of the shift is such that the 50% inhibition of WT cells that is obtained at a concentration of 0.04 μ M requires a concentration of 2.2 μ M for the MDR sub-line, i.e. a 55 fold higher concentration. However, the data depicted in Figure 4 and corresponding reports for low doxorubicin doses [21] indicate that the drug export lowers the intracellular concentration only by a factor of about 2. This means that some other factors must be responsible for the MDR resistance that corresponds to additional 20-30 fold drug concentration change. From the data in Figure 3A we also learn that both the MDR and WT cells are similarly highly sensitive to combined chemotherapy - TTFields treatments. Thus, while a 50% inhibition of MDR cells by doxorubicin alone requires a concentration of 2.2 μ M, the combined treat-

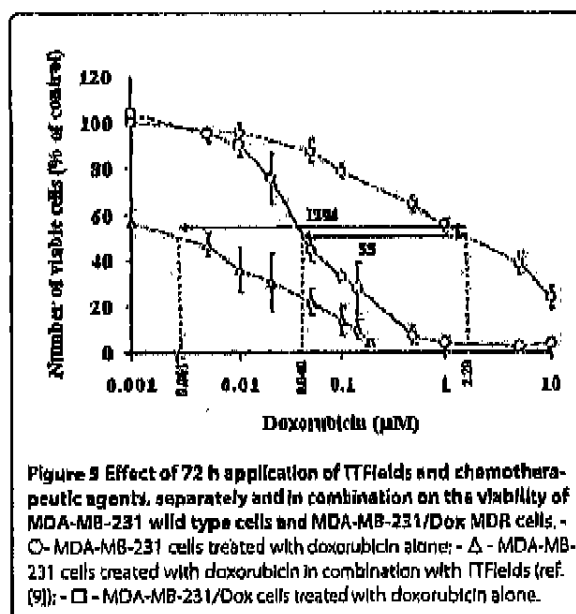


Figure 5 Effect of 72 h application of TTFields and chemotherapeutic agents, separately and in combination on the viability of MDA-MB-231 wild type cells and MDA-MB-231/DOX MDR cells. - \circ - MDA-MB-231 cells treated with doxorubicin alone; - Δ - MDA-MB-231 cells treated with doxorubicin in combination with TTFields (ref. [9]); - \square - MDA-MB-231/DOX cells treated with doxorubicin alone.

ment of TTFields and low concentration of doxorubicin (0.0017 μ M) is sufficient to induce a similar inhibition. This is equivalent to an increased intracellular concentration of doxorubicin by a factor of over 1000. Thus, TTFields seem to have effects specific to MDR cells, not related to drug transport, that increase the MDR cell's sensitivity to chemotherapy. This conclusion is consistent with that of others [22-24] that attribute the MDR resistance, in addition to reduced drug uptake, to a number of potential mechanisms such as: sugar metabolism and energy production, alterations in cytoskeletal elements, microtubule and mitochondria distribution, etc. Within the framework of the above suggested mechanisms [22-24] it seems that the integrity of cytoskeleton and microtubule as well as the mitochondria distribution may be the most vulnerable to the forces produced by TTFields. The former may be disrupted by particle movements induced by the dielectrophoresis induced during TTFields application [8] while the latter are highly polar in themselves and are therefore directly subjected to the alternating field forces.

Conclusions

The results of this study support the notion that TTFields may be used, both as an effective stand alone anti-proliferation agent for MDR cells, as well as an effective adjuvant that enhances chemotherapy efficacy. Furthermore, since TTFields are a physical modality, their therapeutic efficacy is independent of interaction with cell receptors. Therefore their efficacy is not expected to be limited to a specific set of cell types [8-12]. On the basis of the above, we believe that there is a high probability that TTFields

may prove to be an effective therapeutic modality to a wide range of human cancers including those that developed multi drug resistance.

List of abbreviations

MDR: multidrug resistance; TTFields: tumor treating electric fields; DRI: dose reduction index; WT: wild type.

Competing interests

RSS, ES and EK are employees of NovoCure Ltd. YP has a minority holding in NovoCure Ltd.

Authors' contributions

YP: Conceived the concept of TTFields, designed experiments, was involved in data analysis & interpretation of results and wrote the majority of the manuscript. RSS: Participated in experimental design, supervised the experiment execution, analyzed results and wrote parts of the manuscript. ES: Carried out the experiments. EK: Participated in experimental design and in the interpretation of the results.

All authors read and approved the final manuscript.

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Research article

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Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields)

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Abstract

Background: The present study explores the efficacy and toxicity of combining a new, non-toxic, cancer treatment modality, termed Tumor Treating Fields (TTFields), with chemotherapeutic treatment in-vitro, in-vivo and in a pilot clinical trial.

Methods: Cell proliferation in culture was studied in human breast carcinoma (MDA-MB-231) and human glioma (U-118) cell lines, exposed to TTFields, paclitaxel, doxorubicin, cyclophosphamide and dacarbazine (DTIC) separately and in combinations. In addition, we studied the effects of combining chemotherapy with TTFields in an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients.

Results: The efficacy of TTFields-chemotherapy combination in-vitro was found to be additive with a tendency towards synergism for all drugs and cell lines tested (combination Index ≤ 1). The sensitivity to chemotherapeutic treatment was increased by 1–3 orders of magnitude by adjuvant TTFields therapy (dose reduction indexes 23 – 1316). Similar findings were seen in an animal tumor model. Finally, 20 GBM patients were treated with TTFields for a median duration of 1 year. No TTFields related systemic toxicity was observed in any of these patients, nor was an increase in Temozolomide toxicity seen in patients receiving combined treatment. In newly diagnosed GBM patients, combining TTFields with Temozolomide treatment led to a progression free survival of 155 weeks and overall survival of 39+ months.

Conclusion: These results indicate that combining chemotherapeutic cancer treatment with TTFields may increase chemotherapeutic efficacy and sensitivity without increasing treatment related toxicity.

Background

A new physical cancer treatment modality termed Tumor Treating Fields, or TTFields, has recently been demonstrated to be highly effective when applied to cell cultures, animal cancer models, as well as to patients suffering from locally advanced and/or metastatic solid tumors [1-3]. In a pilot clinical trial, the medians of time to disease progression and overall survival of recurrent GBM patients treated by TTFields alone were more than double the reported medians of historical control patients [1]. In contrast to the widely used physical treatment modality, ionizing radiation, TTFields are not associated with significant side effects.

TTFields are low intensity (1–2 V/cm), intermediate frequency (100 – 200 kHz) alternating electric fields generated by special insulated electrodes applied to the skin surface. These specially tuned fields have no effect on quiescent cells while having an anti-mitotic effect on dividing cells. During cytokinesis, TTFields generate non-uniform intracellular fields that exert forces that move polar macromolecules and organelles towards the narrow neck, separating the newly forming daughter cells, by a process termed dielectrophoresis. These molecular and organelle movements, together with an interference with the spindle tubulin polymerization process, inhibit cell division and lead to cell death [2]. Fortunately, the dividing cells of the hematopoietic system are not affected by TTFields as the muscles surrounding the marrow containing bones serve as an effective electric field shield. Moreover, due to their relatively high frequency range and very low intensity, TTFields do not stimulate nerves and muscles, do not generate meaningful temperature elevation or puncture the cell membrane (as the strong electroporation fields do [4]). Thus, TTFields are not associated with meaningful toxicity in contrast to most anti-cancer agents currently in use [5].

In view of the unfavorable therapeutic indexes of the available effective chemical and physical (i.e. ionizing radiation) therapeutic agents, many cancer treatment protocols require simultaneous or sequential use of a number of therapeutic agents in an attempt to increase efficacy while maintaining tolerable toxicity [5-7]. Within this framework it is generally accepted that by adding ionizing radiation [8] to chemotherapy one gets both the benefit of the radiation effect as well as sensitization leading to an increased efficacy without a corresponding increase in toxicity. On the basis of the above this study explores the potential use of the new physical treatment modality, TTFields, in combination with chemotherapeutic agents in cell cultures, an animal tumor model, as well as in patients with glioblastoma (GBM). As TTFields are not associated with systemic toxicity [1] the expectation is that their addition will result in an increase in efficacy alone.

Methods

Cell cultures

Cells were cultured and maintained as previously described [1,2]. In brief: Human breast cancer (MDA-MB-231) and human glioma (U-118) obtained from ATCC (USA) were cultured in DMEM + 10% FCS media in a 5% CO₂ incubator at 37°C. Drops consisting of 200 µl suspension of cells (100 × 10³ cells/ml) were placed at the centre of 35 mm Petri dishes, incubated for 2 hours to allow for cell attachment, then 1.5 ml of media were added and incubation was continued for an additional 22 h. Following this, the baseline cell count was estimated using the XTT colorimetric method (expressed as OD₀). The media in the Petri dishes was replaced by fresh media (3 ml), with or without a chemotherapeutic agent and incubated at a final temperature of 37° ± 0.5°C for 24 to 72 hours after which the cell number was re-estimated (OD₁). The relative number of viable cells at each time point following baseline was expressed as OD₁/OD₀ and treatment efficacy as the % change in proliferation relative to control:

$$(OD_1/OD_0)_{\text{experiment}} * 100 / (OD_1/OD_0)_{\text{control}} \quad (1)$$

TTFields treatment of cultures

As previously described [1,2], two pairs of electrodes, insulated by a high dielectric constant ceramic, were positioned normal to each other at a distance of 20 mm in treatment and control dishes. In the former, the electrodes were connected to sinusoidal waveform generator that generated fields of optimal frequencies in the medium [1,2,9]: 150 kHz for breast cancer and 200 kHz for glioma, that changed direction by 90° every 250 ms. Field intensity was measured as described previously [2] and expressed as V/cm. For 72 h experiments the TTFields intensity of 1.75 V/cm was used. For 24 h experiments 0.65, 1.25 and 1.75 V/cm TTFields were used.

Four different sets of experiments were conducted in conjunction with each chemotherapeutic agent: untreated (sham control), treatment with TTFields, treatment with the chemotherapeutic agents, and combined TTFields + Chemo treatment.

Assessment of combination index and dose reduction index

The Chou and Talalay [10] method for assessing the combined effect of multiple drugs was used for the drug – TTFields combinations. In order to assess whether the interactions between TTFields and each of the chemotherapeutic agents is synergistic, additive or antagonistic, combination indexes were calculated as follows: TTFields intensity replaced the concentration (dose) variable in the analyses. Dose-response curves were generated for TTFields and each drug to determine the median effect

points. Variable ratios of drug concentrations to TTFields intensities were used to calculate the Combination Indexes (CI) as follows:

$$CI = (C_{Drug(incubination), X\% effect} / C_{Drug(alone), X\% effect}) + (I_{TTFields(incubination), X\% effect} / I_{TTFields(alone), X\% effect}) \quad (2)$$

Where: C are the drug concentrations and I the TTFields intensities use to achieve a preset X% effect. Relationships of $CI < 1$ indicate more than additive – synergy, $CI = 1$ reflects additivity – summation and $CI > 1$ indicates less than additive or antagonism.

In order to assess whether TTFields increase the sensitivity of tumor cells to various chemotherapeutic agents, the dose reduction index (DRI) of for each of these agents was calculated according to [11]. In short, the median-effect plots were for each chemotherapy-TTFields combination, were constructed. The ratio of affected to unaffected number of cells (f_u/f_0) was plotted versus drug concentration on a log-log scale. The median effect point (D_m) was assessed by deriving the slope of the linear regression for each of the plots. The DRI for a 50% effect (DRI_m) was calculated as the ratio of D_m for drug alone and for combined drug-TTFields:

$$DRI_m = D_{m(drug alone)} / D_{m(combined treatment)} \quad (3)$$

A DRI greater than 1 indicates an increase in sensitivity to the drug. The greater the DRI, the more significant the possible dose reduction.

In-vivo experiments

Combined TTFields and Paclitaxel efficacy study in VX2 tumor bearing rabbits was conducted after approval by the NovoCure Internal Animal Care and Use Committee. All painful or anxiogenic procedures were performed under general anesthesia induced by intramuscular administration of 30 mg/kg of ketamine hydrochloride, 10 mg/kg xylazine hydrochloride and 1.5 mg/kg Acepromazine. The tumor tissue required for implantation was obtained from VX-2 tumor bearing carrier rabbits. The carrier rabbits had VX-2 tumors implanted intramuscularly in the thigh. When the tumor reached approximately 1 cm in diameter (about 3 weeks from implantation), the tumor was excised, minced in sterile saline and VX-2 tumor fragments obtained. Two fragments were injected using a large bore needle into the thigh muscles of both legs in a recipient rabbit for tumor propagation. For experimental animals, after laparotomy, a fragment of tumor tissue (1 mm³) was implanted beneath the kidney capsule of the recipient rabbit.

The current experiment comprised 28 animals (7 in each of 4 groups). Fourteen days after tumor implantation the

initial tumor volume was assessed based on serial (2.2 mm interval) T1 weighted axial MRI images (1.5 Tesla, GE Genesis-Signa) obtained 3 minutes following IV injection of 3 ml of Gadolinium. Tumor volume was assessed from the area of the contrast enhancing lesion in each section. The animals were assigned randomly into 4 groups before treatment start:

1. TTFields treated group: TTFields were applied by using the NovoTTF-100A device (NovoCure LTD., Haifa, Israel). An optimal frequency of 150 kHz and intensity of 1–2 V/cm were used. TTFields were switched sequentially between two perpendicular field directions.

2. Control group: sham electrode heated to mimic heat generated by the TTFields treatment. (38–39.9 °C)

3. Paclitaxel (Medixel Injection., Taro Pharmaceutical Industries LTD., Israel) treated group: 5 mg/animal diluted in 100 ml of normal saline were infused intravenously over a period of 30 minutes. Premedication was given subcutaneous 8 hours before and immediately prior to Paclitaxel administration (Dexamethasone (Dexaveto-0.2 veterinary, V.M.D n.v/s.a Belgium) 0.5 mg/animal; Pramirine (Metoclopramide HCL, Rafa Laboratories LTD., Israel) 1 mg/animal; Diphenhydramine (10%, Medical M., Israel) 10 mg/animal).

4. Combined TTFields and Paclitaxel treatment as above.

TTFields were delivered to awake and behaving rabbits through four insulated electrode arrays placed circumferentially around the animal's abdomen, caudal to the ribcage. The electrode insulation consisted of a high dielectric constant (>10,000) ceramic (PMN-PT) allowing efficient energy transfer through the insulation into the animals body at the given frequencies. The electrodes were connected by a spiral cable to a swivel mechanism at the top of the cage, enabling the free movement. TTFields were generated using the NovoTTF-100A system (NovoCure Ltd., Haifa, Israel). The animals were treated for 21 days continuously with MRI performed on days 14 and 21 for tumor volume assessment. The TTFields intensity within the kidneys of the rabbits, using this electrode configuration, is between 1–3 V/cm (based on both finite element mesh simulations and direct measurements using an invasive probe – data not shown).

Pilot clinical trial

A single arm, pilot trial of the safety and efficacy of TTFields treatment was performed in 20 patients with histologically proven glioblastoma multiforme (GBM) that met the inclusion/exclusion criteria specified in Supplemental Material Appendix A (briefly, KPS 70–100%, Age ≥ 18). The trial was performed according to a protocol

approved by the Na Homolce Institutional Review Board and the Czech Republic Ministry of Health. The patients were divided into two groups: The first group included 10 patients with recurrent GBM treated with TTFields alone following failure of maintenance Temozolomide [1]. The second group consisted of 10 newly diagnosed patients who were at least 4 weeks post radiation therapy, who received TTFields combined with maintenance Temozolomide. Prior to initiation of treatment, all patients underwent a baseline contrast MRI of the head, chest radiograph, EEG, ECG, complete blood & urine analyses, physical examination and neurological status. The patients were hospitalized for 1–3 days for observation and then released home where they received multiple 4-week courses of continuous NovoTTF-100A treatment until progression. The patients were seen once/month at an outpatient clinic where they underwent an examination similar to the initial one. TTFields were applied to the patients using the NovoTTF-100A device set to deliver 200 kHz, 0.7 V/cm (RMS) fields (at the center of the brain) in 2 perpendicular directions, 1 second in each direction sequentially. The TTFields were applied continuously using four insulated electrode arrays, each having a surface area of 22.5 cm², placed on opposing sides of the head with the tumor positioned directly between the electrode pairs [1]. As previously reported, to avoid electrolysis at the electrode surface and intracellular ion concentration changes that accompany long term current application, the electrodes were completely insulated by a ceramic having a very high dielectric constant (>10,000) that allowed the generation of the necessary electric fields [1,2]. Using this electrode configuration, the lowest TTFields intensity at the center of the brain was 0.7 V/cm (RMS). This intensity was calculated using finite element mesh simulations and verified by direct measurement in large animals and a human volunteer [1].

The outcome endpoints of the study included safety, overall survival (OS) and progression free survival (PFS). Assessment of tumor response was based on monthly MRIs according to the Macdonald criteria [12]. Median OS and PFS were determined using Kaplan Meier curves [13]. In the first group, PFS in NovoTTF-100A treated patients was compared to a matched group of concurrent control patients who received salvage chemotherapy at recurrence (n = 18). PFS in Temozolomide/NovoTTF-100A treated patients was compared to the PFS of a

matched group of concurrent control patients (n = 32) who received Temozolomide alone (according to the protocol described by Stupp et al. [14]). OS in both groups was compared to matched historical control data with the same Karnofsky performance score (>60) and age [14].

Results

Breast cancer cell cultures

Dose – response of culture exposure to TTFields, paclitaxel, doxorubicin and cyclophosphamide, alone and in combination

The relationship between TTFields intensity, at 150 kHz, and cell proliferation rate is given in Figure 1A. At the lowest field intensity of 0.63 V/cm there is no significant change in cell proliferation. For TTFields intensities of 1.25, 1.75 and 2.95 V/cm cell proliferation decreases (control = 100%) to: $90 \pm 3\%$, $74 \pm 4\%$ and $25 \pm 5\%$, respectively. The dose-response curves of cells exposed to paclitaxel, doxorubicin and cyclophosphamide, alone and in combination with 1.75 V/cm TTFields for 72 hours, are given in Figures 1B, C & D. For each drug alone there is a decrease in cell proliferation with increase in concentration. For cyclophosphamide and doxorubicin complete inhibition of proliferation is achieved at high drug concentrations. For paclitaxel, the inhibitory effect of the drug saturates at about 300 nM, near the 13% level, indicating that a fraction of the cells are insensitive to the agent. Combined treatment with TTFields and each of the chemotherapeutic agents caused a leftward shift of the dose response curves. This shift can be expressed as a decrease in the drug concentration leading to 50% inhibition of cell proliferation (IC₅₀ – Table 1).

Time course of the effects TTFields, paclitaxel, doxorubicin and cyclophosphamide

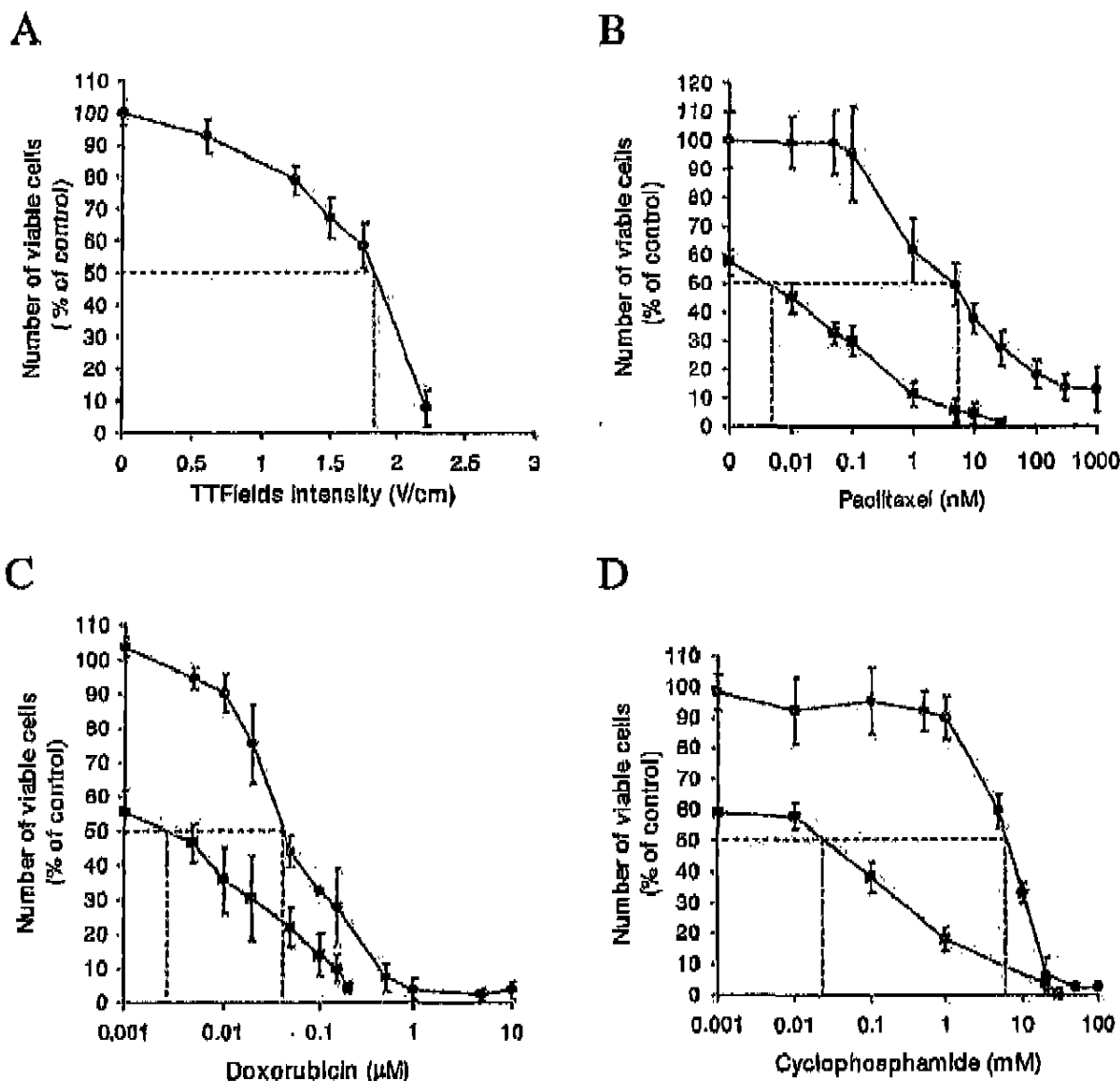
Figure 2 displays the time course of proliferation inhibition during a continuous 72 hour exposure to TTFields, paclitaxel, doxorubicin and cyclophosphamide alone and in combination with 1.75 V/cm TTFields. It is seen that in all cases the inhibition during combined exposure is greater than for the chemotherapeutic agent alone. The differences between the separate and combined effects increase with time.

Recovery from treatment

Figure 3 demonstrates that a 24 hour exposure to individual chemotherapeutic agents induces a reduction of approximately 25% in viable cell number compared to

Table 1: IC₅₀ for chemotherapeutic drugs alone and in combination with 1.75 V/cm TTFields after 72 hours of continuous treatment.

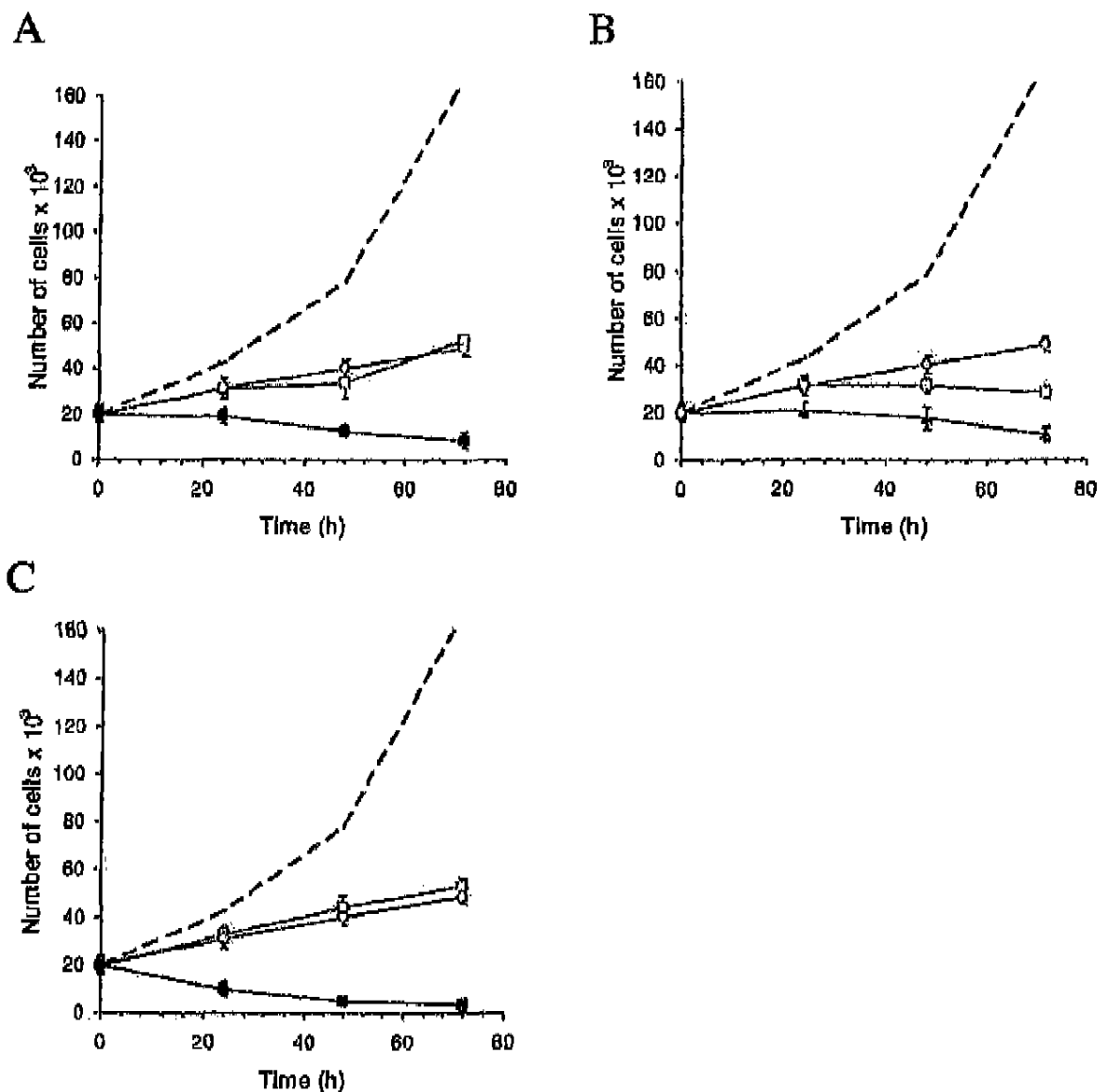
Chemotherapy	IC ₅₀ (drug alone)	IC ₅₀ (drug-TTFields combination)
Paclitaxel	5.00 nM	0.005 nM
Doxorubicin	0.04 μM	0.002 μM
Cyclophosphamide	6.60 mM	0.044 mM

**Figure 1**

Effect of 72 hour continuous application of TTFields and chemotherapeutic agents, separately and in combination on the cell proliferation of ER-negative MDA-MB-231 cells (presented as percent viable cells compared to control). (A) Percent viable cells vs. TTFields intensity. Effect of different concentrations of paclitaxel (B), doxorubicin (C) and cyclophosphamide (D), alone and in combination with TTFields of 1.75 V/cm. In B, C and D Filled Circles – represent drug alone; Filled Squares – drug in combination with TTFields. Each point represents mean values \pm SEM of 10 to 36 replicate measurements. Dotted lines demarcate the IC₅₀ values for each curve.

controls. The proliferation rate (slope of the graph) recovers almost completely during the following 48 hours, except for doxorubicin, where recovery is slower and

delayed by about 24 hours. In contrast, addition of TTFields to any one of these chemotherapeutic agents results in irreversible and complete inhibition of cell pro-

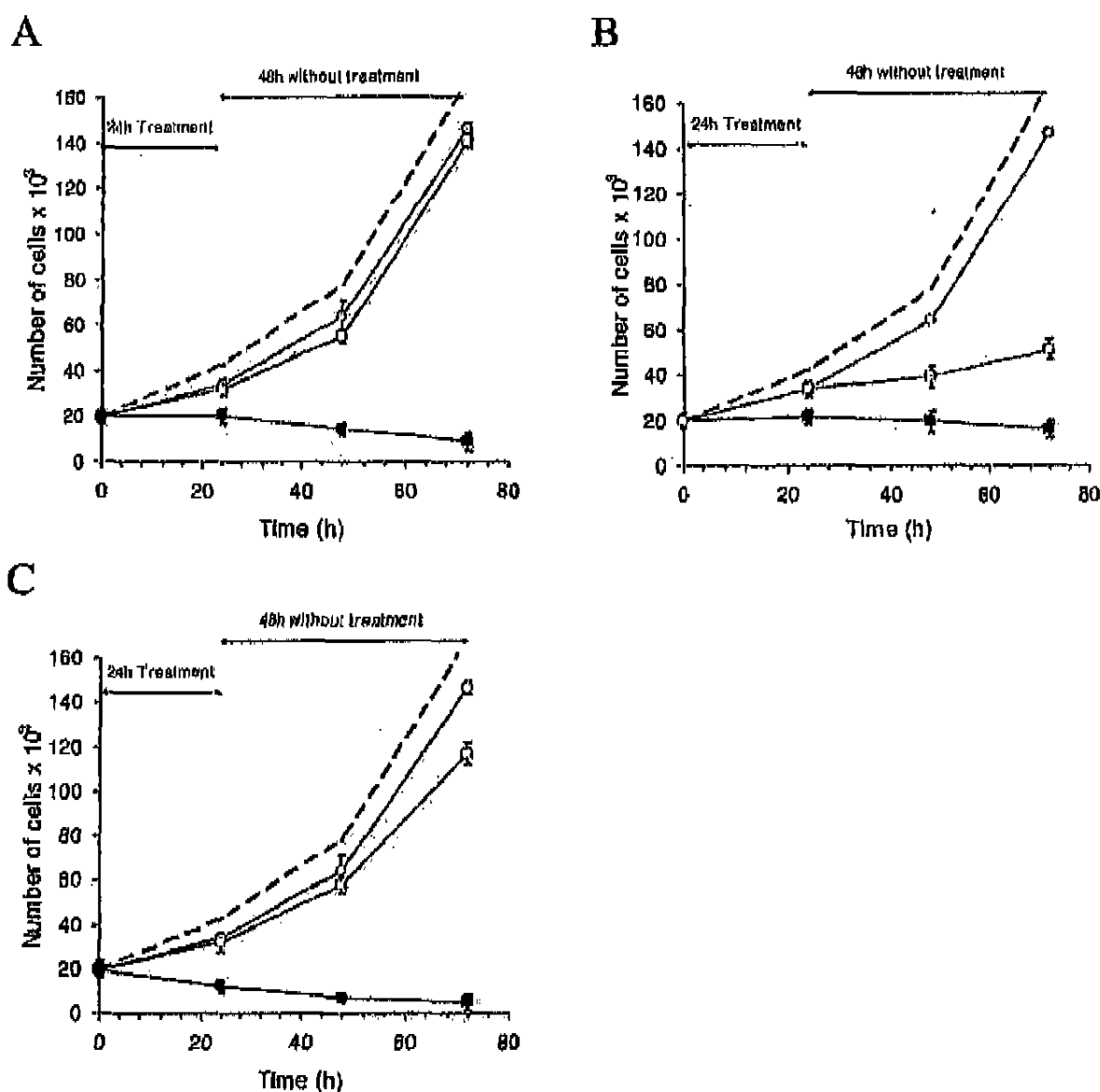
**Figure 2**

Time course of the effects of 72 hour exposure of MDA cells to Paclitaxel (A), Doxorubicin (B) and Cyclophosphamide (C) alone and in combination with 1.75 V/cm TTFields. Each graph shows the number of viable cells in culture over time in control cells (interrupted lines), drug alone (open squares), TTFields alone (open circles) and drug-TTFields combination (closed squares). Data are presented as mean \pm SEM. Each experimental condition included 18-36 samples.

liferation rate manifested as a decrease in the number of cells in culture. For Cyclophosphamide there is an almost complete loss of viable cells after 72 hours of combined treatment.

Glioma cell cultures

Combined effect of DTIC and TTFields in human glioma cell cultures
In order to assess the combination between Temozolomide and TTFields in glioma cells, DTIC and TTFields

**Figure 3**

Time course of recovery from 24 hour exposure to Paclitaxel (A), Doxorubicin (B) and Cyclophosphamide (C) alone and in combination with 1.75 V/cm TTFields. Each graph shows the number of viable cells in culture over time in control cells (interrupted lines), drug alone (open squares), TTFields alone (open circles) and drug-TTFields combination (closed squares). Data are presented as mean \pm SEM. Each experimental condition included 18–36 samples.

were applied alone and in combination to U-118 cells in culture. Both DTIC and Temozolomide act through a common degradation product (MTIC). Thus light activated DTIC was used for these experiments as described

previously [15,16]. Figure 4 compares the DTIC dose-response curve, with that obtained with DTIC - TTFields combination. As we have shown in breast cancer cultures, the addition of TTFields to a chemotherapeutic agent

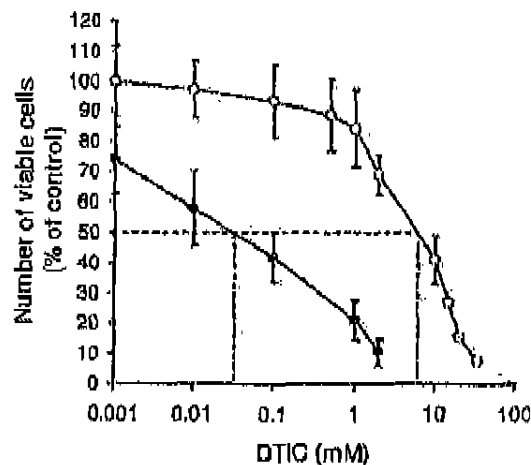


Figure 4
Effect of light activated DTIC and TTFIELDS (1.75 V/cm) on cell proliferation of U-118 glioma cells, presented as percent of viable cells compared to control. Open Circles - 72 hours of DTIC treatment alone. Filled Circles - 72 h of Combined DTIC - TTFIELDS treatment.

causes a leftward shift in the dose-response curve in glioma cells as well. The IC_{50} for DTIC alone in Figure 4 is 6.4 mM, whereas the IC_{50} for combined DTIC-TTFIELDS is two orders of magnitude lower (0.023 mM).

Analysis of combination efficacy and sensitivity in-vitro Combination indexes

The mode of interaction between TTFIELDS and chemotherapeutic agents (synergism, additivity or antagonism) can be analyzed using Combination Indexes (CI) as described by [10,17]. In order to calculate the CIs for TTFIELDS-Chemotherapeutic agents, the extent of inhibition of cell growth was assessed after 24 hours of treatment with Paclitaxel, Doxorubicin and Cyclophosphamide alone or in combination with different intensities of TTFIELDS (0.625–1.75 V/cm; see Materials and Methods). Table 2 demonstrates that for breast cancer cells the CI for Doxorubicin is very close to 1, indicating additivity [10,11]. In contrast, for TTFIELDS with Paclitaxel and Cyclophosphamide the CIs are <1 indicating additivity with a tendency towards synergism.

Dose reduction indexes

In order to assess the extent of possible chemotherapeutic dose reduction when applied in combination with TTFIELDS, dose reduction indexes (DRI) for each drug-TTFIELDS combination were calculated based on the meth-

Table 2: Calculated Combination Indexes for human breast cancer (MDA-MB-231) cells treated with paclitaxel, doxorubicin or cyclophosphamide in combination with TTFIELDS.

TTFIELDS Intensity (V/cm)	Combination Index		
	MDA-MB-231 cells		
	Paclitaxel	Doxorubicin	Cyclophosphamide
	CI_{40}	CI_{50}	CI_{50}
0.625	-	-	0.74
1.25	0.97	0.99	0.84
1.75	0.86	0.98	0.95

odology described by [11]. The DRIs for TTFIELDS-drug interaction after 72 hours of combined treatment was 1316 for paclitaxel, 29 for doxorubicin, 152 for cyclophosphamide and 175 for DTIC (in U-118 glioma cells). Thus a significantly reduced dose (1–3 orders of magnitude lower drug concentration) may be used in combination with TTFIELDS to achieve the same level of efficacy.

Effect of combined paclitaxel and TTFIELDS on VX2 tumors in rabbits

Prior to testing the combined efficacy of paclitaxel and TTFIELDS on VX2 tumors implanted within the kidneys of rabbits, the dose-response of paclitaxel in this animal tumor model was determined. A dose of Paclitaxel leading consistently to a 15–20% inhibition in tumor growth (5 mg/rabbit) was chosen for subsequent combination experiments with TTFIELDS.

As seen in Figure 5, untreated tumors increased in volume by a factor of 70 from baseline. Paclitaxel treated tumors grew by a factor of 58 from baseline, TTFIELDS treated tumors grew by a factor of 34 from baseline and tumors treated by TTFIELDS-Paclitaxel combination grew by a factor of 22 from baseline. Thus the TTFIELDS-Paclitaxel combination treatment inhibited tumor growth by 69% compared to the growth of control tumors, while Paclitaxel alone inhibited tumor growth by 15% compared to the growth of control tumors, and TTFIELDS alone by 53% compared to the growth of control tumors. Thus, additivity was seen between TTFIELDS and Paclitaxel at the intensity and concentration used. Differences between curves were statistically significant ($p < 0.01$; ANOVA).

Pilot clinical trial in GBM patients

Twenty patients with histological diagnosis of GBM were treated continuously for an average of 1 year (range 2.5–24 months). Ten recurrent GBM patients were treated with TTFIELDS alone as salvage therapy. Ten newly diagnosed

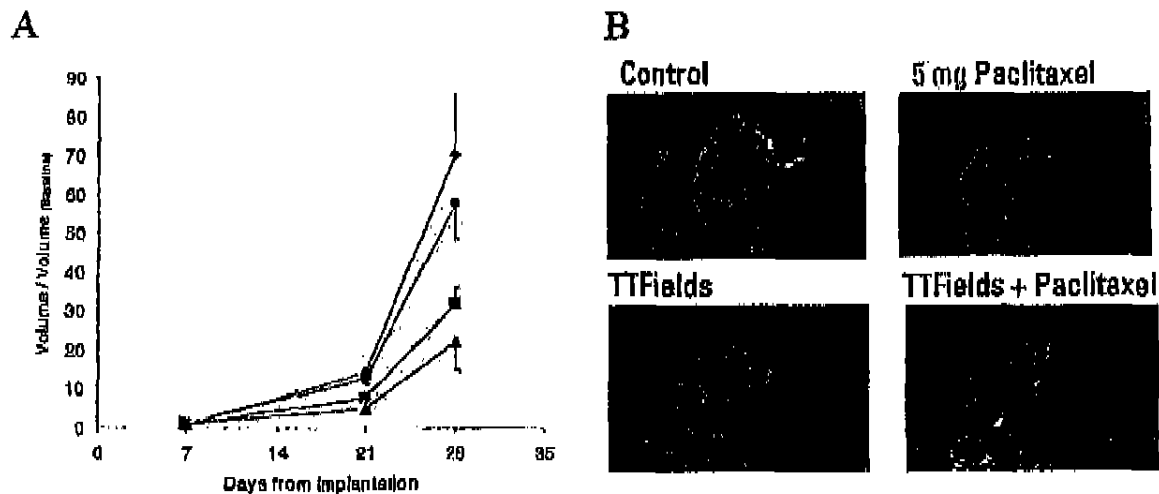


Figure 5
Effect of combined Paclitaxel/TTFields on VX2 tumors in Rabbits. A VX-2 Kidney tumor volumes were normalized to pre-treatment tumor volume (day 7) and are presented over time for: control (diamonds), 5 mg Paclitaxel (circles), TTFields (squares) and combined TTFields-Paclitaxel (triangles). The effect of combined TTFields and Paclitaxel is equal to the sum of the effects of either treatment alone at both time points measured during the study (2 and 3 weeks from treatment start; $n = 23$; bars are standard errors of means). B Exemplary MRIs of the maximal contrast enhancing tumor area (demarcated by orange borders) in the kidneys of rabbits in each of the experimental groups (sham control, Paclitaxel 5 mg, TTFields 2 V/cm, combined Paclitaxel and TTFields).

GBM patients, that had undergone surgery and thereafter received radiation therapy with adjuvant Temozolomide, were treated with the combination of TTFields in parallel to maintenance Temozolomide [14]. In both groups of patients no device related serious adverse effects were observed. The only device related toxicity reported was a dermatitis which appeared most often (18 of 20 patients) during the second month of treatment. The severity of the dermatitis decreased upon use of topical corticosteroids and periodic electrode relocation. The dermatitis continued for the duration of treatment and resolved completely within days to weeks from treatment termination.

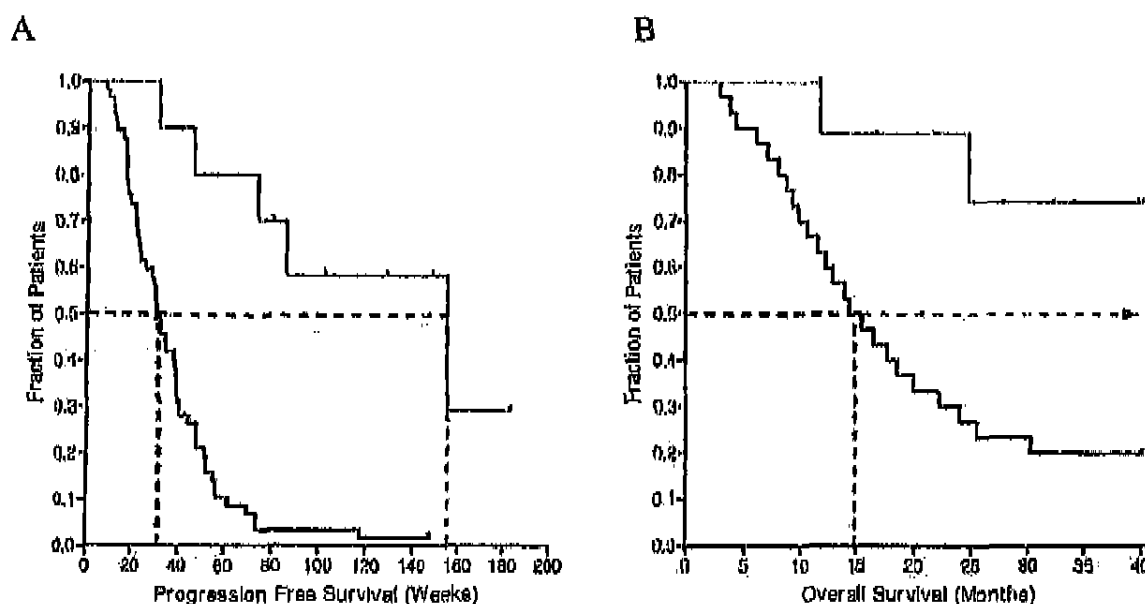
In the second group, no increase in Temozolomide related adverse events was seen due to the combination with TTFields (see Table 3).

As reported previously [1], both progression free survival (PFS) and overall survival (OS) in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively. The efficacy of the TTFields-Temozolomide combination in the second group of patients was assessed using Kaplan Meier curves [13] of PFS and OS. The Kaplan Meier curves for the PFS of these patients, treated by combined TTFields - Temozolomide are shown in Figure 6A. The median PFS of the

combination treated patients is 155 weeks versus 31 weeks for concurrent controls treated with maintenance Temozolomide alone. Note that 5 of 10 patients are currently progression free. Figure 6B compares the OS of the patients that received the combination treatment (red line) with a matched historical control (KPS ≥ 60 , Median age 54) (black line [14]). It is seen that for the TTFields - Temozolomide combination treated patients, the Median OS > 39 months versus about 14.7 months for matched historical control patients who received maintenance Temozolomide alone. It should be noted that at the time

Table 3: Toxicities by grade and causality in the newly diagnosed GBM patients treated with combined TTFields-Temozolomide.

	Grade		Causality assessment
	I-II	III-IV	
Elevated LFTs	6/10	0/10	Anti Epileptic Drugs
Hyperglycemia	4/10	0/10	Oral Steroids
Anemia	6/10	0/10	Temozolomide
Thrombocytopenia	2/10	0/10	Temozolomide
Leucopenia	3/10	0/10	Temozolomide
Headache	2/10	0/10	Underlying disease
Seizures	1/10	0/10	Underlying disease
Dermatitis	10/10	0/10	NovoTTF-100A

**Figure 6**

Kaplan Meier curves for A – progression free survival (PFS) and B – overall survival (OS) of newly diagnosed GBM patients receiving either combined TTFields – Temozolomide treatment or Temozolomide treatment alone. Red line – patients receiving combined TTFields – Temozolomide treatment (n = 10). Black line – concurrent/historical control patients that received Temozolomide treatment alone. A – The difference between the PFS curves is highly significant – Log-Rank Test ($P = 0.0002$), Hazard Ratio 3.32 (95%CI 1.9–5.9). B – The difference between the OS curves is highly significant – (Log-Rank Test; $P = 0.0018$). Dashed lines mark the median values for each curve.

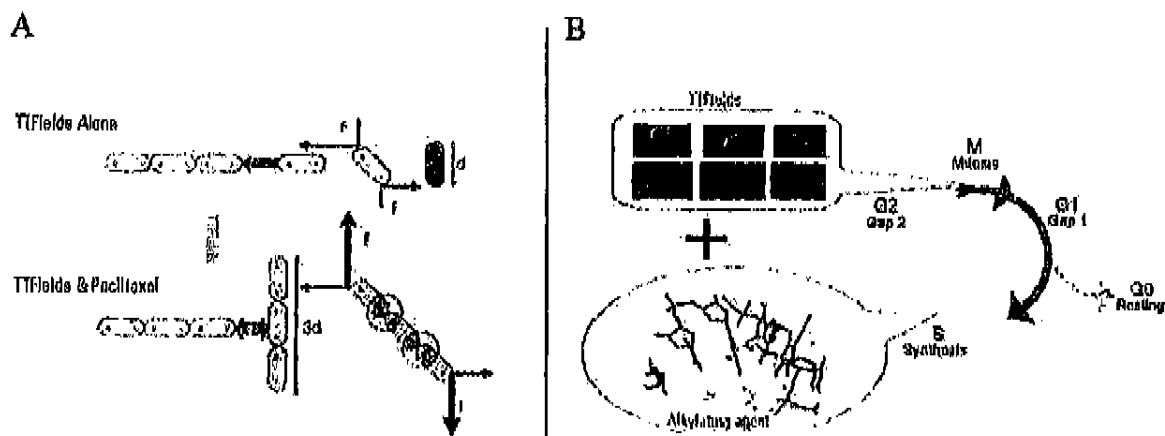
of this report 8 of 10 patients, receiving the TTFields-Temozolomide combination treatment, are alive.

Discussion

Cancer treatment with drug combinations was introduced in order to improve therapeutic indexes through dose reduction of each drug and increase treatment efficacy. In this study the exposure of cancer cells to combined chemotherapy and TTFields was studied in cell cultures, an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients. The results of this study support the possibility that TTFields may be used, not only as an effective stand alone anti-proliferation agent (as shown previously [in 1]), but also as an effective adjuvant that enhances chemotherapy efficacy without an increase in toxicity. In addition to this increase in efficacy, these results raise the possibility of dose reduction of chemotherapy when used in combination with TTFields. This is of utmost importance since, at tolerable doses the efficacy of available cancer therapeutic agents is often far from optimum while being associated with a high degree of toxicity.

With regards to the mechanisms involved, one may assume that tumor cells are sensitized to TTFields by chemotherapy, much like another well established physical therapy – ionizing radiation [8,18,19]. In the specific case of Paclitaxel, one of the most commonly used treatments for late-stage human breast cancer [20], the combined effect may be attributed to their similar site of action – the spindle microtubules [1,2,21]. Taxanes act by stabilizing the link between individual tubulin dimers [21]. As illustrated schematically in Figure 7A taxanes increase the length of tubulin filaments within the cell. One of the mechanisms of action of TTFields is the misalignment of mitotic spindle filaments as a result of TTFields forces on tubulin chains [2]. The increase in filament length due to taxanes, increases the dipole moment of these macromolecules, leading to an increase in the TTFields induced forces and thus to a higher sensitivity of the cell to TTFields (see Figure 7A).

Doxorubicin that has a broad spectrum of activity both in experimental tumor models and in human malignancy, affects both DNA and RNA syntheses [22]. Cyclophosphamide (an alkylating agent) inhibits DNA replication by

**Figure 7**

Mechanisms of potentiation of chemotherapeutic efficacy by TTFields. A Tubulin chains are elongated by Paclitaxel, leading to an increase in the average dipole moment of free tubulin chains (d – length of an individual tubulin dimer; f – force between the microtubule chain and the dimer; F – force acting on the tubulin dimmers by TTFields; Arrow length is proportional to the intensity of these forces). The forces TTFields exert on these larger dipoles, F , are enhanced leading to an increase in the disruption of the mitotic spindle by TTFields. B TTFields act as an M-phase inhibitor, while alkylating agents act at the G and S phases of the cell cycle. This separation between cell cycle phases affected explains the additivity seen experimentally.

interfering with the separation of the double stranded DNA essential for transcription [23]. As illustrated in Figure 7B, since TTFields act at a completely different stage (M phase) of the cell cycle from both these agents, additivity between chemotherapy and TTFields can be expected.

Since the data for newly diagnosed GBM patients, which points to well over a 300% increase in PFS and OS, was obtained only with combination treatment, one cannot directly separate the TTFields effects from the chemotherapeutic effect. However, if we assume that the TTFields therapeutic efficacy for newly diagnosed patients is similar to recurrent GBM, i.e. the median of OS is increased by 270% [1] while the published Temozolomide data indicates an increase of about 20% in OS compared to ionizing radiation treatment alone [14], the results presented in Figure 6 point towards additivity between TTFields and Temozolomide. It is important to note that this significant increase in efficacy was obtained without any increase in device or drug related toxicity (see table 3).

An additional important finding is that both 24 h and 72 h combination treatments in-vitro result in severe irreversible cellular damage in contrast to chemotherapy alone. This result strengthens the assumption that combination therapy with TTFields may be much more effective than treatment by individual agents.

Conclusion

The results of the present study support the notion that TTFields may be used clinically not only as an anti-proliferation agent as shown before [1], but also as effective sensitizers of currently used chemotherapeutic agents. Such sensitization was not shown to be associated with any additional systemic toxicity. Moreover, as demonstrated by the high DRIs calculated in this study, chemo/TTFields combinations are expected to provide the same or even greater therapeutic efficacy with much lower drug concentrations thus lowering further the overall toxicity.

Competing interests

EK, RSS, AI, DM, ZG, ES and YW are employees of NovoCure Ltd.

YP has a minority holding in NovoCure Ltd.

VD, FT, JV and DG have no competing interests.

Authors' contributions

EK – planned the pre-clinical and clinical experiments, supervised their execution, analyzed results and wrote parts of the manuscript. RSS and ET – Performed the in-vitro experiment and assisted in the in-vivo experiments. DM, ZG and AI – Performed the in-vivo experiments. DG – Performed the MRI imaging for the in-vivo experiments. YW – Planned the medical devices and treatment parameters.

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ters for all experiments. VD, FT and JV – performed the clinical trial in GBM patients (clinical investigators). YP – invented the concept of TTFs, helped interpret all results and wrote the majority of the manuscript.

Appendix

Appendix A – Eligibility criteria for the pilot GBM trial

Inclusion criteria:

Histologically proven diagnosis of GBM,

Age over 18 years,

Karnofsky scale ≥ 70 .

Participants of child bearing age had to be receiving efficient contraception.

Willing and able to sign an informed consent prior to participation in the study.

Exclusion criteria:

Patients actively participating in another clinical trial

Patients who received any anti-tumor therapy in the four weeks prior to trial initiation (steroids are permitted; however, the dose must be stable or decreasing during the trial).

Patients suspected of suffering from radiation necrosis (according to a PET scan).

Pregnancy

Patients with one of the following co-morbidities:

Patients with an implanted pacemaker or documented arrhythmias,

Significant renal, hepatic or hematologic disease.

Significant additional neurological disorder:

Seizure disorder unrelated to the patient's tumor

Pre-existing dementia

Progressive degenerative neurological disorder

Meningitis or encephalitis

Hydrocephalus associated with increased intracranial pressure (ICP)

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Review

Expert Opinion

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Tumor treating fields: concept, evidence and future

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Introduction: Local control is fundamental, both for the curative as well as the palliative treatment of cancer. Tumor treating fields (TTFields) are low intensity (1 – 2 V/cm), intermediate frequency (100 – 200 kHz) alternating electric fields administered using insulated electrodes placed on the skin surrounding the region of a malignant tumor. TTFields were shown to destroy cells within the process of mitosis via apoptosis, thereby inhibiting tumor growth. TTFields have no effect on non-dividing cells.

Areas covered: This article reviews *in vitro* and *in vivo* preclinical studies, demonstrating the activity of TTFields both as a monotherapy as well as in combination with several cytotoxic agents. Furthermore, it summarizes the clinical experience with TTFields, mainly in two indications: one in recurrent glioblastoma multiforme: in a large prospective randomized Phase III trial TTFields was compared with best standard care (including chemotherapy); TTFields significantly improved median overall survival (OS) compared with standard therapy (7.8 vs 6.1 months) for the patients treated per protocol. Importantly, quality of life was also better in the TTFields group. The second indication was a Phase II study in second-line non-small cell lung cancer, where TTFields was administered concomitantly with pemetrexed. This combination resulted in an excellent median OS of 13.8 months. Interestingly, the progression-free survival (PFS) within the area of the TTFields was 28, however, outside the TTFields the PFS was only 22 weeks.

Expert opinion: The proof of concept of TTFields has been well demonstrated in the preclinical setting, and the clinical data seem promising in various tumor types. The side effects of TTFields were minimal and in general consisted of skin reaction to the electrodes. There are a number of ways in which TTFields could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible. While more clinical data are clearly needed, TTFields is an emerging and promising novel treatment concept.

Keywords: cancer, electric fields, glioblastoma, non-small cell lung cancer, TTFields

Expert Opin. Investig. Drugs [Early Online]

1. Background

Alternating electric fields have been used since many years for the diagnosis, research and treatment of various medical conditions. Such electric fields have different properties, depending on their frequency and intensity (Table 1). Very low frequencies (lower than 1 kHz) are used to excite the membrane of muscles and nerves, thereby leading to membrane depolarization and finally to action potentials (1–3). Higher frequency alternating electric fields penetrate cells better, but the overall effect of hyper-depolarization on the cell membrane balances in a way that the integrated stimulation does not yield an action potential. However, at frequencies higher than 10 MHz, the electrophysiological properties of the eukaryotic

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Article highlights.

- Tumor treating fields (TTFields) are low intensity (1 – 2 V/cm), intermediate frequency (100 – 200 kHz) alternating electric fields, which can induce apoptosis.
- TTFields are able to inhibit tumor growth in various cell lines and animal models.
- The combination of TTFields with several cytotoxic agents resulted in a supra-additive tumor growth inhibition *in vitro* and *in vivo*.
- Two clinical trials, a Phase III trial in glioblastoma multiforme (GBM) and a Phase II study in non-small cell lung cancer (NSCLC) have shown antitumor activity of TTFields.
- Toxicity was low; it consisted mainly of skin reactions at the site of the electrodes.

This box summarizes key points contained in the article.

membrane lead to dielectric polarization that eventually heats the tissue [4,5]. Intermediate-frequency alternating electric fields, at frequencies between 10 kHz and 1 MHz, neither cause net depolarization nor significant dielectric losses, therefore, cannot stimulate nerves/muscles, but also cannot seriously heat tissues at low enough intensities. It was thought that such electric fields have no meaningful biological effect on cells [4,6-9]. Nevertheless, it was recently found that such fields, named tumor treating fields (TTFields), have an anti-mitotic activity and may lead to the death of dividing cells. The fields were found to have these properties already at a very low intensity (< 2 V/cm) and at intermediate frequency of 100 – 300 kHz.

2. TTFields's mechanism of action

Each cell contains numerous electrically charged molecules, such as proteins and DNA. Under an alternating electric field, these molecules will oscillate according to the changing direction of the field and its density (Figure 1). If the field is uniform, the forces acting intermittently to opposite directions will cause a movement parallel to the direction of the field. When the frequency of the field is high enough, such as in the case of TTFields, this molecular movement will reduce. In the case of dipoles, where there is an electric split between the positive and negative poles of a molecule, it will align with the direction of the electric field and remain at the same place. All charged molecules, including dipoles, will move toward the higher field density in a non-uniform alternating electric field. Within a non-dividing cell, the field is mostly uniform and the net force on charges and dipoles will, therefore, yield minimal movement. Non-uniform electric fields, on the other hand, force polar molecules to move toward higher field intensity, in a process called dielectrophoresis [10,11]. Such fields are characteristic of dividing cell when a narrow furrow connects the two forming daughter cells.

2.1 Arrest of mitotic spindle formation

Mitotic spindle is the organelle that separates the cell's chromosomes to each of the daughter cells during mitosis. The arms that hold to the chromosomes consist of small polar molecules called tubulins, which polymerize to form a 'chain' of subunits that will reach the genetic material at the center of the cell. As noted before, the field is uniform within the non-dividing cells, but the tubulin subunits will tend to align according to the direction of the field. Finite element simulations showed that the electrical forces acting on the subunits prevent them from attaining the orientation required for efficient polymerization, therefore, mitosis becomes arrested for an abnormally long time [12]. This happens since subunits far enough from the growing microtubule will be subjected to an electric force strong enough to prevent further polymerization. When this process takes place, cells could either complete mitosis or deintegrate.

2.2 Mitotic furrow destruction

Not all cells seem to be affected by means of disruption of mitotic spindle formation. The membranes of cells that completed metaphase will start dividing into two daughter cells, pulling the daughter chromosomes to each of the cells' poles. During the last step in mitosis, that is, cytokinesis, a cleavage furrow is eventually formed, which completes the process of cell separation. This narrow membranous link results in an hourglass-shaped non-uniform electric field, unlike non-dividing cells, in which the electric field is uniform. During cytokinesis, the densest electric field is found in the narrow center. This focusing of the field directs all electric charges and dipoles to the furrow due to the unidirectional character of the electric force (dielectrophoretic force) under this condition. Finite element simulations have shown that polarized molecules and organelles within the cell will be affected by forces high enough to move toward the furrow so as to disrupt the internal cell structure and cause the cell destruction seen under TTFields therapy [12].

3. Preclinical studies with TTFields

A number of preclinical trials have shown the efficacy of TTFields in the inhibition of cancer cell proliferation and their destruction *in vitro* [12,13]. Many cell lines were cultured and tested under TTFields, among others melanoma, glioma, lung, prostate and breast cancers. TTFields was applied continuously for 24 – 72 h, in all cases, proliferation was significantly inhibited, compared with control cultures and to non-replicating cultures (baby hamster kidney (BHK) cells) treated with TTFields. For some of the cell lines, a specific optimal frequency that demonstrated maximal inhibitory effect was found, possibly reflecting different cell size and shape (Table 2) [13]. Under time-lapse microscopy, cancer cells demonstrated significantly prolonged mitosis and even cell destruction on the formation of the cleavage furrow. Immunohistochemistry studies of cell cultures treated with TTFields showed many abnormal

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Table 1. Alternating electric fields used in medicine

Frequency	Biological activity	Application
< 1 kHz	Membrane depolarization	Defibrillators, ECT, bone growth, fracture healing, ICD
100 - 300 kHz	Mitotic arrest and apoptosis	TTFelds
1 - > 10 MHz	Dielectric polarization	Diathermy, radio frequency tumor ablation

ECT, electroconvulsive therapy; ICD, implantable cardioverter-defibrillator; TTFelds, tumor treating fields.

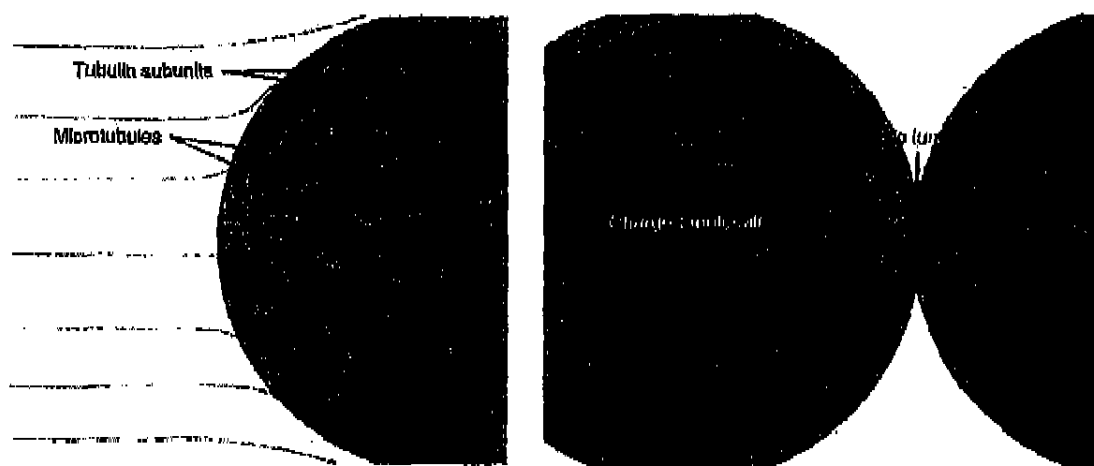


Figure 1. Antimitotic effects of tumor treating fields (TTFelds). At the beginning of mitosis, the electric field is uniform within the cell, causing tubulin subunits to align with the direction of the field and inhibiting their polymerization to form a normal microtubule spindle. In a non-uniform electric field formed during cytokinesis, charges and dipoles move toward the high field density at the mitotic furrow, disrupting mitosis and disintegrating the daughter cells.

mitotic figures that could be related to the interference of TTFelds with the mitotic spindle formation. These figures resemble the presentation of cancer cells treated with agents that interfere with mitotic spindle formation, such as paclitaxel. Further experiments showed that the efficacy of TTFelds in combination with different chemotherapies is additive and could be synergistic (14).

Interestingly, TTFelds caused cultured cells to orient in the direction of the electric field (12). This could be explained by the fact that the electric forces are maximal when the axis of division is aligned with the external field. This also implies that the angle of the cell affects its vulnerability to TTFelds during mitosis.

TTFelds was also shown to inhibit tumor growth in several mouse, rat and rabbit animal models (12,15). Implanted cell lines were used to test the most effective frequency and intensity for this *in vivo* treatment. Postmortem analysis of the treated animals showed a significant tumor size reduction in the case of TTFelds-treated animals, compared with control animals. No difference of the local temperature in the vicinity of the tumor was found between the two groups. *In vivo* experiments showed that it is possible to deliver the field to the target region using

insulated non-invasive electrodes. While there was no statistically significant inhibition of tumor growth when a unidirectional TTFelds was delivered this way, two- and three-directional fields led to a statistically significant growth inhibition (19). *In vivo* tumor models have shown the same optimization in tumor inhibition when using the effective specific frequency for each cell type. No abnormality in vital signs, electrocardiograms (ECG), complete blood counts (CBC), chemistry and coagulation panels was found during the follow-up period of animals treated with TTFelds, and no treatment-related pathologies were found postmortem.

In a metastatic melanoma mouse model and metastatic kidney cancer rabbit model, TTFelds was shown to reduce the extent of metastatic spread, possibly due to metastasis growth inhibition, migration capability impairment and primary tumor local control (19).

4. Clinical studies with TTFelds

Prior to applying TTFelds to human patients, feasibility was tested using finite element method (FEM) simulations and measurements within the brain of a volunteer undergoing brain

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Table 2. Optimal TTFs frequency for tested cell lines

Cell line	Optimal frequency (kHz)
B16F1 (mouse melanoma)	120
AA8 (Chinese hamster ovary)	150
VX-2 (rabbit kidney)	150
MCF-7 (human breast)	150
MDA-MB-231 (human breast)	150
F-98 (rat glioma)	200
U-87 (Human glioma)	200
U-118 (Human glioma)	200

TTFs, tumor treating fields.

surgery. It was found that TTFs can be effectively applied to the cerebrum using surface electrodes. TTFs was first tested on 10 recurrent malignant glioblastoma multiforme (GBM) patients. No concomitant chemotherapy was used during the clinical trial, and TTFs was the only antitumor therapy. TTFs was delivered via a portable, light-weight (~ 3 kg) device carried by the patient (NovoTTFs-100A, NovoCure Ltd, Haifa, Israel), connected to two pairs of insulated electrodes that were applied to the patients' skin. The device continuously (18 h/day on average) delivered two perpendicular 1–2 V/cm, 200 kHz alternating electric fields (Figure 2). Patients had a highly significant increase in the median time to disease progression (26.1 weeks) and progression-free survival (PFS) at 6 months (50%) compared with historical controls, with a median overall survival (OS) of more than 62 weeks (13). In addition, no treatment-related serious adverse event was detected in a total of 280 treatment weeks. The only treatment-related adverse event was mild-to-moderate contact dermatitis beneath the electrode gel, which was easily managed using topical treatments.

These preliminary findings led to a Phase III clinical trial of TTFs compared with best standard of care chemotherapy in 237 patients with recurrent GBM (16,17). Patients in this study were previously treated with an unlimited number of surgeries/chemotherapy cycles. They were randomized to either a TTFs arm, given as a monotherapy without additional antitumor treatments, or to the best standard chemotherapy (BSCh) arm, which was at the treating physician's discretion. TTFs was administered continuously and patients' compliance was excellent, with a median duration of 20 h/day. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. Mean treatment duration was 4.4 months in the TTFs group versus 2.3 months in the BSCh group. In the group of 185 patients who were treated per protocol, a statistically significant survival benefit was seen for the TTFs group (median OS 7.8 vs 6.1 months for TTFs and BSCh, respectively). Moreover, patients with better prognostic baseline characteristics (KPS 80% or higher, age 60 or lower) demonstrated an even higher survival benefit when treated with TTFs (median OS 8.8 vs 6.6 months; $n = 110$). These results show that TTFs

as a monotherapy are at least as effective as the best available chemotherapy or supportive care in this poor prognosis disease. It is noteworthy that quality of life (QOL) was equivalent or superior in patients treated with TTFs compared with BSCh. This clinical trial also showed that the only TTFs-related adverse events were mild-to-moderate contact dermatitis beneath the electrodes in a minority of patients. The incidence of toxicities was significantly higher in the BSCh arm.

TTFs was also explored in a Phase I/II single arm study in combination with pemetrexed for advanced (stage III/IV) non-small cell lung cancer (NSCLC) as a second-line treatment, after failure of standard first-line chemotherapy (18). Electrodes were applied to the chest and upper abdomen and the device (NovoTTFs-100 L, NovoCure Ltd) generated 150 kHz TTFs, in accordance with the preclinical findings relating to lung cancer cell lines. Forty-one patients were treated, including 7 (17.1%) with squamous cell carcinoma and 30 (73%) with stage IV disease. The device was well tolerated and the average daily use was 11.2 h. No TTFs-related serious adverse event was reported for a cumulative time of over 720 weeks. Median PFS was 22 weeks and in-field PFS (i.e., PFS within the area of the TTFs; the study's primary end point) in the lungs and liver was 28 weeks. This is an important finding because it can be assumed that in the same patient the higher tumor control within the TTFs area was a specific effect of TTFs. Median OS was 13.8 months and 1-year survival was 57% (Figure 3). Six patients (14.6%) had a radiological partial remission (PR) and 16 patients had stable disease (SD) (39%). These results are very promising and compare extremely well with matched historical controls treated with pemetrexed alone in second-line treatment (19).

Special attention was given to potential adverse events using TTFs: in the glioblastoma trial careful neurological examination and documentation was required once a month. In the lung cancer trial, ECGs were mandated at the beginning of the trial, during the treatment if adverse effects occurred and at the end. Finally, skin reactions were monitored at every visit and documented according to the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC) (version 3.0) in all studies. All other adverse events were monitored routinely at every visit according to the CTC criteria. In all studies involving TTFs the only side effect, which occurred more frequently was grade 1–2 skin toxicity. In the glioblastoma trial there was a direct control group, in the lung cancer trial we compared the side effects with the large Phase III study by Hanna *et al.*, in which pemetrexed was given as a second-line treatment (19).

5. Summary

TTFs was shown to inhibit proliferation and to cause cell destruction of many cancer cells *in vitro* and *in vivo*. In addition, TTFs significantly improved human patients' prognosis in recurrent GBM and probably also in NSCLC. At the time this review was submitted, there were no serious adverse events found related to TTFs.

end points were excellent, compared with historical data for pemetrexed alone [19].

The good safety profile along with the significant clinical efficacy and QOL advantages make TTFields an attractive treatment in GBM, and perhaps in many other malignancies.

6. Expert opinion

TTFields is a novel and promising concept for treating solid tumors. *In vitro* and *in vivo* experiments have repeatedly shown a significant inhibitory effect on cancer cell proliferation upon application of TTFields. We already know that at least two physical mechanisms are involved: the first is interference with the mitotic spindle formation as a result of electric forces preventing the normal polymerization of the tubulin subunits. The second mechanism results from the non-uniformity of the electric field in the context of cytokinesis, and the movement of molecules in the direction of the mitotic furrow as a result of the unidirectional force generated by TTFields.

There are also some data indicating that combining chemotherapeutic cancer treatments with TTFields may increase efficacy and sensitivity to chemotherapy [14]. Several tumor types are sensitized to radiation after adding different chemotherapies, even at low doses [24-26]. Could some tumors similarly be more susceptible to TTFields treatment if treated concomitantly with certain cytotoxic agents? This is a plausible idea, since TTFields acts on specific organelles (e.g., the mitotic spindle), which are also the target of some of the anticancer drugs. Taxanes act through stabilizing the link between tubulin dimers in the spindle microtubules. It could be that the abnormal increase in microtubule length caused by this class of agents, which leads to the formation of a larger dipole moment, results in an increase in the efficacy of TTFields [14]. This possible synergism could be used to achieve a better response, but alternatively also as a way to decrease chemotherapy intensity in patients who cannot tolerate the toxicity of full-dose chemotherapy. The fact that TTFields itself was not toxic and in combination with pemetrexed did not increase the known side effects of the latter in the clinical trials mentioned above, makes combination therapies an attractive therapeutic option.

Preclinical experiments showed the frequency-dependant effect of TTFields, with different frequencies showing a maximal inhibitory effect in certain cancer cell types [18]. In the future, it will be interesting to see how this characteristic could be exploited in order to maximize the effect, by adjusting the frequency on an individual tumor basis, using cytological/pathological specimens for the analysis. Such adjustments could be possible for tumors of the same entity but in different patients, and maybe even at different stages in the course of the same disease.

Other fields of interest that will probably be investigated in the future include the pathway in which cell death occurs following exposure to TTFields. Unpublished findings show that apoptosis is the process that leads to cancer cell death



Figure 2. The tumor treating fields (TTFields) generating portable device (NovoTTFields-100A).

On the contrary, the treatment was toxicity-free for treated patients, except for mild-to-moderate contact dermatitis underneath the electrodes. Importantly, there were no cardiac or neurological abnormalities as a result of TTFields treatment. The use of non-invasive surface electrodes prevented flow of ionic currents [20,21] or cell death [22] as a result of direct currents, and thus decreased skin damage and enabled continuous treatment.

TTFields can actively inhibit different cell types, including multi-drug-resistant (MDR) ovarian and breast cancer cell lines that overexpress ABC (ATP-binding cassette) transporters [23]. It may not only be useful in the treatment of locally advanced tumors, but also in the prevention and treatment of metastatic disease. TTFields has the potential to inhibit the migration of metastases from a primary tumor; it can inhibit the growth of metastases in the lungs once they have been seeded in the target organ, through the presence of the fields in the lungs themselves.

In the first Phase III study published to date [16,17], TTFields had minimal toxicity and patients' compliance was excellent, over an extended period of time. The application of TTFields resulted in an improved median OS, higher response rate and longer time to treatment failure compared with best standard chemotherapies and also led to an improvement in many QOL parameters. A large-scale Phase III clinical trial in newly diagnosed GBM is currently being conducted.

In the first clinical trial for NSCLC patients, TTFields was well tolerated in a second-line setting. It was safe and efficacy

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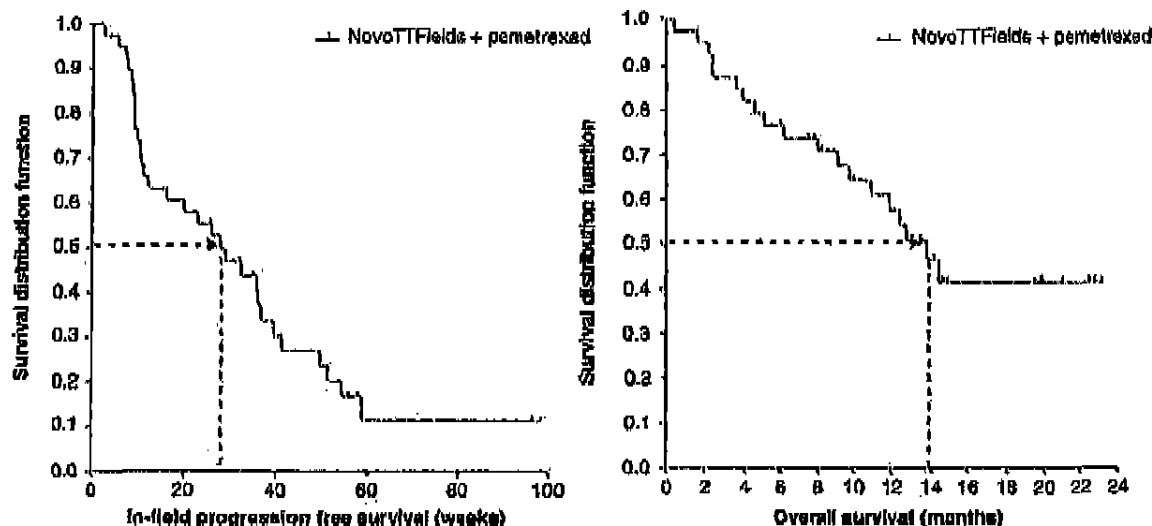


Figure 3. Phase II trial using tumor treating fields (TTFields) in combination with pemetrexed in non-small cell lung cancer as a second-line therapy. Median in-field progression-free survival (PFS) was 28 weeks. Median overall survival (OS) was 13.8 months; $n = 41$.

Adapted from poster presentation ESMO 2010 [18].

under TTFields. Finding the specific pathway through which apoptosis is carried out will provide a better understanding of the basic mechanism and will pave the way for other combinations or treatment optimization. The immune system plays an important role in the pathogenesis of cancer [27]. TTFields has the potential to beneficially affect the microenvironment of the tumor: it could act directly on recruited immune cells, alternatively, it could change the interaction between these cells and the tumor following changes to the tumor cell structure, vasculature, etc. Preliminary data show that there is a change in the presence of immune cells that interplay with cancer cells, following TTFields treatment [15].

Both the Phase III (for recurrent GBM patients) and the Phase II (for advanced NSCLC) trials have given some important insights on using TTFields [16–18]. The high compliance demonstrates that it is feasible to administer TTFields continuously using a light-weight portable device, in spite of the necessity to be attached to the device. Since most patients enrolled in the trials were somewhat hindered by their malignant disease, they generally adjusted to TTFields quite quickly and well. In the NSCLC trial, the majority of patients used TTFields overnight and was free at daytime. It can be assumed that other cancer patients will tolerate TTFields as well. It will be interesting to see how other chemotherapies administered concomitantly to TTFields will affect the course of these patients. A Phase III trial (NCT00916409) for newly diagnosed GBM patients treated with a combination of temozolomide and TTFields is currently ongoing.

As a physical treatment modality, TTFields has the potential to be active in other solid tumors as well. In a pilot study,

TTFields therapy was very well tolerated and safe for four patients bearing skin lesions from breast and melanoma tumors. These tumors showed transient inhibition in the growth rate during a 2- to 4-week treatment and the findings warrant further investigations [28]. While systemic chemotherapy usually has significant toxicities, biologically targeted therapies often affect only a subset of tumors carrying specific mutations or proteins. Glioblastoma and NSCLC, like many other tumors, harbor many different genotypes [29–31] and it has been difficult to show a major impact of chemotherapy or even targeted agents in these tumor types, at least for the majority of patients. TTFields acts independently of the expression of cell surface receptors or other tumor biomarkers. There are no alternative mitosis mechanisms, thus cancer cells are unlikely to be or to become resistant to TTFields.

There are several ways of further developing TTFields clinically. TTFields is a regional treatment: it could be employed in situations where radiotherapy is not possible anymore, for example, after a full course of radiation to the brain. Another option would be to test it in situations in which prophylactic radiotherapy is used: for example, prophylactic cranial irradiation (PCI) small cell lung cancer, hopefully circumventing the late toxicity of PCI. Lastly, it can of course be tested together with radiotherapy. Even though TTFields is a regional treatment, it still managed to decrease the likelihood of metastases formation in animal experiments [15], the most common cause of death in cancer. It could be that TTFields was able to prevent malignant cell evasion from the primary tumor in the lung cancer treated population, thereby leading to decreased formation of micrometastases [18].

In summary, TTFields could be considered as a potential effective treatment for patients suffering from different cancer types. The non-toxic characteristics and promising clinical outcomes in several clinical trials conducted to date should encourage investigators to further evaluate TTFields, either as a monotherapy or in combination with other treatments.

Declaration of Interest

M Pless declares no conflicts of interest. U Weinberg works for NovoCure Ltd. as Medical Director. Novocure has supported experiments described in this review and was the sponsor for the clinical trials. The paper was not supported by a commercial company.

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**Medicare
Managed Care & PACE
Reconsideration Project**

**Reviewing
Medicare Appeals**

MAXIMUS Federal Services
Medicare Part C QIC
3750 Monroe Ave, Suite 702
Pittsford, New York 14534
Tel: 585-348-3300
Fax: 585-425-3392
www.medicareappeal.com

Who We Are

We are MAXIMUS
Federal Services. We are
experts on appeals.
Medicare hired us to review
the file and decide if the
health plan made the correct
decision. We work for
Medicare. We do not work
for the health plan.

Katy Hansen
Project Director
Medicare Managed Care &
PACE Reconsideration
Project

Do you need help?

Call 1-800-MEDICARE
(1-800-633-4227) for help or
more information about what
you can do in this case. TTY
users should call 1-877-486-
2048.

JULY 2, 2013

RE:

Medicare Number: [REDACTED]

Date: [REDACTED]

This letter is about our decision in your appeal to ANTHEM BLUE CROSS LIFE
AND HEALTH INS COMPANY (Anthem). You asked Anthem to pre-approve
the NovoTTF 100-A system (electrical field therapy) for [REDACTED]

Our decision

We agree with you. This means that we will tell Anthem to pre-approve the
NovoTTF 100-A system. To learn more about how we made our decision,
read the following pages of this letter.

What you have to do

We sent Anthem a copy of this letter, so they know they have to pre-approve
the NovoTTF 100-A system.

Make sure the NovoTTF 100-A system is obtained through Anthem.
Otherwise, Anthem may not pay for it.

Anthem has to pre-approve the item or service or make plans to pre-approve
the item or service within 72 hours. If Anthem does not do so within 72
hours, call the Chicago CMS Regional Office at 312-753-7180.

Chicago CMS Regional Office

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How we made our decision

1. We read all the papers in the file.
2. We checked Medicare rules.
3. We checked the contract with Anthem.
4. We sent the file to a MAXIMUS Federal Services Doctor Consultant.

To make our decision we read all the papers in the file very carefully. We used the Medicare rules. We looked to see if Anthem correctly followed Medicare rules and regulations.

Medicare rules say that the health plan must give the member a subscriber agreement. It is a contract between the health plan and the member. It is usually called the "Evidence of Coverage" (EOC) or "Member Agreement." We read this contract carefully to see what Anthem is supposed to cover.

We sent the case to a MAXIMUS Federal Services Doctor Consultant. This doctor works for us, not the health plan. We asked this doctor to review all of the medical records in the file.

Medicare rules

The rules say that health plans must pay for a medical service or item if regular Medicare would pay for it in this case. You can find this rule at 42 CFR §422.101.

The rules say that medically necessary services are those that are reasonable and necessary for the diagnosis or treatment of an illness or injury. Medically necessary services include services to improve the functioning of a malformed body member. You can find this rule at Social Security Act § 1862 (a)(1)(A).

If you want to read these Medicare rules, you can go to this web site www.medicareappeal.com.

The health plan contract

The health plan contract says that Anthem covers items and services in accordance with Medicare rules.

Doctor review

Our MAXIMUS Federal Services Doctor Consultant looked at the file for this case. This doctor says that the NovoTTF 100-A system is medically necessary for [REDACTED]. Our doctor found that the patient presented in October 2012 with headache, confusion and left hemiparesis. A MRI scan revealed a right fronto-temporal mass that was resected by December 2012. The pathology showed this tumor was a glioblastoma multiforme, WHO grade IV. She got temozolomide and concurrent radiation therapy but the tumor progressed. She had more surgery in March 2013 after which the NovoTTF device was recommended. In 2011, the FDA approved the NovoTTF-100A device to deliver alternating electrical fields to treat recurrent GBM. The device has FDA approval and is appropriate to use in this patient who has exhausted standard chemotherapy options.

Explanation of decision

We decided that Anthem has to pre-approve the NovoTTF 100-A system (electrical field therapy) for [REDACTED].

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You asked Anthem to pre-approve the NovoTTF 100-A system. You say that this device is the only promising option for the patient at this time. Due to her orphan disease status, limited treatment options and favorable outcome and higher quality of life afforded with this treatment, you are requesting that the patient be covered with this device. ~~There is no evidence in the literature that this device is superior to the current standard of care.~~
Evidence is 2B (equivocal) in the current NCCN guidelines which is not sufficient to warrant medical necessity.

Anthem must follow Medicare rules. Medicare rules say that if there are no specific coverage rules for an item or service, then that item or service will be covered when it is medically necessary.

Our MAXIMUS Doctor Consultant says that the NovoTTF 100-A system is medically necessary for [REDACTED]. We looked at this doctor's review, the file and Medicare rules. Based on this information, we decided that Medicare rules for coverage of the NovoTTF 100-A system have been met. Therefore, we decided that Anthem has to pre-approve the NovoTTF 100-A system (electrical field therapy) for [REDACTED].

If Anthem does not agree with our decision, they can ask us to open a case again. We only open a case again if we believe there was a mistake or if there is new information to review. The health plan has to show us the mistake and/or send us the new information. This does not happen often. If we decide to open the case again, we will send you a letter.

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H

Referral to/from Contractor Medical staff



Contractor Medical Policies

J

LIST OF RELEVANT PORTIONS OF THE LAW, REGULATIONS, CMS RULINGS

LMRP'S

LMRP/LCD

The appropriate Local Medical Review Policy/Local Coverage Determination Number is indicated by an X beside the Number.

____ L11517 Ankle-Foot/Knee-Ankle-Foot Orthosis
[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11517&ContrId=140&ver=66&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11517&ContrId=140&ver=66&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ L13877 Automatic External Defibrillators
[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=13877&ContrId=140&ver=62&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=13877&ContrId=140&ver=62&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ L4989 Canes and Crutches
[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=4989&ContrId=140&ver=37&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=4989&ContrId=140&ver=37&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ L15905 Cervical Traction Devices
[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=15905&ContrId=140&ver=39&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=15905&ContrId=140&ver=39&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ L11552 Cold Therapy
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____ L4991 Commodes
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____ **L11518Continuous Positive Airway Pressure System (CPAP)**
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____ **L11553Enteral Nutrition**
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____ **L11554External Breast Prostheses**
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____ **L11555External Infusion Pumps**
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____ **L11519Eye Prosthesis**
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____ **L11556Facial Prostheses**
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____ **L11520Glucose Monitors**
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____ **L28614Heating Pads and Heat Lap**
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____ L12934 High Frequency Chest Wall Oscillation Devices
[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=12934&ContrId=140&ver=29&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=12934&ContrId=140&ver=29&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ L11557 Hospital Beds And Accessories
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____ L11521 Immunosuppressive Drugs
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____ L12932 Infrared Heating Pad Systems
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____ L11558 Intrapulmonary Percussive Ventilation System
[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11558&ContrId=140&ver=19&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11558&ContrId=140&ver=19&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ L27259 Intravenous Immune Globulin
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____ L22664 Knee Orthoses
[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=22664&ContrId=140&ver=44&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=22664&ContrId=140&ver=44&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ L11442 Lower Limb Prostheses
[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11442&ContrId=140&ver=60&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11442&ContrId=140&ver=60&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

L11443 Manual Wheelchair Bases

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11443&ContrlId=140&ver=45&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11443&ContrlId=140&ver=45&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

L12930 Mechanical In-exsufflation Devices

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=12930&ContrlId=140&ver=25&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=12930&ContrlId=140&ver=25&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

L5007 Nebulizers

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5007&ContrlId=140&ver=105&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5007&ContrlId=140&ver=105&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

L5008 Negative Pressure Wound Therapy Pumps

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5008&ContrlId=140&ver=51&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5008&ContrlId=140&ver=51&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

L11559 Oral Anticancer Drugs

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11559&ContrlId=140&ver=31&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11559&ContrlId=140&ver=31&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

L1156 Oral Antiemetic Drugs (Replacement for IV Antiemetics)

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11560&ContrlId=140&ver=56&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11560&ContrlId=140&ver=56&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

L28620 Oral Appliances for Obstructive Sleep Apnea

<http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=28620&ContrlId=140>

L11445 Orthopedic Footwear

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11445&ContrlId=140&ver=30&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11445&ContrlId=140&ver=30&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ **L5012 Osteogenesis Stimulators**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=5012&ContrId=140&ver=49&ContrVer=2&CtrctrSelected=140*2&
Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=
Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5012&ContrId=140&ver=49&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ **L5013 Ostomy Supplies**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=5013&ContrId=140&ver=59&ContrVer=2&CtrctrSelected=140*2&
Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=
Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5013&ContrId=140&ver=59&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ **L11446Oxygen and Oxygen Equipment**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11446&ContrId=140&ver=75&ContrVer=2&CtrctrSelected=140*2
&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocTyp
e=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11446&ContrId=140&ver=75&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ **L11561Parenteral Nutrition**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11561&ContrId=140&ver=41&ContrVer=2&CtrctrSelected=140*2
&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocTyp
e=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11561&ContrId=140&ver=41&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ **L11562Patient Lifts**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11562&ContrId=140&ver=38&ContrVer=2&CtrctrSelected=140*2
&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocTyp
e=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11562&ContrId=140&ver=38&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ **L5017 Pneumatic Compression Devices**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=5017&ContrId=140&ver=38&ContrVer=2&CtrctrSelected=140*2&
Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=
Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5017&ContrId=140&ver=38&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ **L23613Power Mobility Devices**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=23613&ContrId=140&ver=46&ContrVer=2&CtrctrSelected=140*2
&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocTyp
e=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=23613&ContrId=140&ver=46&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ **L11563Pressure Reducing Support Surfaces - Group 1**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11563&ContrId=140&ver=34&ContrVer=2&CtrctrSelected=140*2
&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocTyp
e=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11563&ContrId=140&ver=34&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

____ **L11564 Pressure Reducing Support Surfaces - Group 2**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11564&ContrId=140&ver=31&ContrVer=2&CntrctrSelected=140*2
&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType
=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11564&ContrId=140&ver=31&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ **L11565 Pressure Reducing Support Surfaces - Group 3**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11565&ContrId=140&ver=48&ContrVer=2&CntrctrSelected=140*2
&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType
=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11565&ContrId=140&ver=48&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ **L11522 Refractive Lenses**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11522&ContrId=140&ver=35&ContrVer=2&CntrctrSelected=140*2
&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType
=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11522&ContrId=140&ver=35&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ **L5023 Respiratory Assist Devices**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=5023&ContrId=140&ver=65&ContrVer=2&CntrctrSelected=140*2
&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType
=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5023&ContrId=140&ver=65&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ **L11523 Seat Lift Mechanisms**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11523&ContrId=140&ver=32&ContrVer=2&CntrctrSelected=140*2
&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType
=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11523&ContrId=140&ver=32&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ **L11524 Speech Generating Devices**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11524&ContrId=140&ver=31&ContrVer=2&CntrctrSelected=140*2
&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType
=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11524&ContrId=140&ver=31&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ **L11448 Spinal Orthoses: TLSO and LSO**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=11448&ContrId=140&ver=43&ContrVer=2&CntrctrSelected=140*2
&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType
=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11448&ContrId=140&ver=43&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

____ **L5027 Suction Pumps**
[http://www.cms.gov/medicare-coverage-database/details/lcd-
details.aspx?LCDId=5027&ContrId=140&ver=42&ContrVer=2&CntrctrSelected=140*2
&Cntrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType
=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5027&ContrId=140&ver=42&ContrVer=2&CntrctrSelected=140*2&Cntrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCntrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

L11449 Surgical Dressings

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11449&ContrlId=140&ver=58&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11449&ContrlId=140&ver=58&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

L11525 Therapeutic Shoes for Persons with Diabetes

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11525&ContrlId=140&ver=36&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11525&ContrlId=140&ver=36&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

L11526 Tracheostomy Care Supplies

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11526&ContrlId=140&ver=30&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11526&ContrlId=140&ver=30&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

L28616 Transcutaneous Electrical Joint Stimulation Devices (TEJSD)

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=28616&ContrlId=140&ver=3&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=28616&ContrlId=140&ver=3&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

L5031 Transcutaneous Electrical Nerve Stimulators (TENS)

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5031&ContrlId=140&ver=46&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=5031&ContrlId=140&ver=46&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

L34665 Tumor Treatment Field Therapy (TTFT)

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34665&ContrlId=140&ver=3&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34665&ContrlId=140&ver=3&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

L11566 Urological Supplies

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11566&ContrlId=140&ver=52&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11566&ContrlId=140&ver=52&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

L34675 Vacuum Erection Devices (VED)

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34675&ContrlId=140&ver=5&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34675&ContrlId=140&ver=5&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAA%3d%3d&)

L11450Walkers

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11450&ContrId=140&ver=29&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11450&ContrId=140&ver=29&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

L11451Wheelchair Options/Accessories

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11451&ContrId=140&ver=75&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=11451&ContrId=140&ver=75&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

L15887Wheelchair Seating

[http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=15887&ContrId=140&ver=59&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+\(18003%2c+DME+MAC\)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&](http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=15887&ContrId=140&ver=59&ContrVer=2&CtrctrSelected=140*2&Ctrctr=140&name=CGS+Administrators%2c+LLC+(18003%2c+DME+MAC)&DocType=Active&LCtrctr=140*2&bc=AqACAAIAAAAAAA%3d%3d&)

INTERNET ONLY MANUALS (IOM)

<http://www.cms.hhs.gov/Manuals/IOM/list>

100-02 Medicare Benefit Policy

100-03 Medicare National Coverage Determinations Manual

100-04 Medicare Claims Processing Manual

K

Overpayment Extrapolation Materials

L

MRN/Other



Department of Health and Human Services
Office of the Secretary

OFFICE OF MEDICARE HEARINGS AND APPEALS

Miami Field Office
51 SW 1st Avenue, Suite 1536
Miami, FL 33130-1608
786-792-3700 (Main)
786-792-3791 (ALJ Grow Team)
305-536-5044 (Fax)
866-622-0382 (Toll Free)

Date: **JUN 19 2019**

A. PROSSER
W2973 FARMSTEAD DR
APPLETON, WI 54915-8120

NOTICE OF DECISION

Appellant: A. PROSSER
OMHA Appeal Number: 1-8390277469

Enclosed is the decision for the above case. This decision is based on the administrative record, including any evidence or testimony presented at the hearing, if one was held. The decision is not precedential, does not release the appellant from civil or criminal liability, and may be reopened at any time if it was procured by fraud or similar fault. In addition, the decision may be reopened within 180 calendar days from the date of the decision for good cause. Good cause exists when there is new and material evidence that was not available or known at the time of the decision and may result in a different conclusion, or when the evidence that was considered clearly shows on its face that an obvious error was made at the time of the decision.

What if I disagree with the decision?

If you disagree with the decision, you may file an appeal with the Medicare Appeals Council. Other parties may also appeal the decision. In addition, the Medicare Appeals Council may decide to review the decision on its own motion. If no party appeals the decision and the Medicare Appeals Council does not review the decision, the decision is binding on all parties and you and the other parties will not have the right to ask a federal court to review the decision.

If you are not already represented, you may appoint an attorney or other person to represent you.

How much time do I have to file an appeal?

The Medicare Appeals Council must receive your written appeal **within 60 calendar days** of the date that you receive this notice. The Medicare Appeals Council assumes you received this notice 5 calendar days after the date of the notice unless you show that you did not receive it within the 5-day period.

The Medicare Appeals Council will dismiss a late request for review unless you show that you had a good reason for not filing it on time.

How do I file an appeal?

To appeal, you must ask the Medicare Appeals Council to review the decision. Your appeal must be in writing, except that a request for expedited review of a Part D decision may be made orally as described below. Your appeal must identify the parts of the decision that you disagree with, and explain why you disagree.

You may submit a written request for review to the Medicare Appeals Council using one of three available methods: mail, fax, or electronic filing (E-File). **Please do not submit your request for review using more than one method.** Regardless of how you file your appeal, **you must always send a copy of your written request for review to the other parties who received a copy of the decision.**

If you are filing a written request for review, you may use the enclosed *Request for Review* (form DAB-101), or you may write a letter containing the following:

- The beneficiary's/enrollee's name (and telephone number for Part D appeals);
- The beneficiary's/enrollee's Medicare number (Health Insurance Claim Number or Medicare Beneficiary Identifier);
- The item(s), service(s), or specific Part D drug(s) in dispute;
- The specific date(s) the item(s) or service(s) were provided, if applicable;
- For Part D appeals, the plan name;
- For Part D appeals, the OMHA Appeal Number on the adjudicator's decision;
- For Part D appeals requesting expedited review, a statement that you are requesting expedited review;
- The date of the adjudicator's decision (not required for Part D appeals); and
- Your name and signature, and, if applicable, the name and signature of your representative.

Filing by mail:

Mail your appeal and a copy of the enclosed decision to:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

Filing by fax:

Fax your appeal and a copy of the enclosed decision to **(202) 565-0227**.

Filing by computer:

Using your web browser, visit the Medicare Operations Division Electronic Filing System (MOD E-File) website at <https://dab.efile.hhs.gov/mod>.

To file a new appeal using MOD E-File, you will need to register by:

- (1) Clicking **Register** on the MOD E-File home page;
- (2) Entering the information requested on the “Register New Account” form; and
- (3) Clicking **Register Account** at the bottom of the form.

You will use the email address and password you provided during registration to access MOD E-File at <https://dab.efile.hhs.gov/mod/users/new>. You will be able to use MOD E-File to file and access the specific materials for appeals to which you are a party or a party’s representative. You may check the status of any appeal on the website homepage without registering.

Once registered, you may file your appeal by:

- (1) Logging into MOD E-File;
- (2) Clicking the **File New Appeal** menu button on the top right of the screen;
- (3) Selecting the type of appeal you are filing (Request for Review or Request for Escalation); and
- (4) Entering the requested Appeal Information and uploading the requested Appeal Documents on the “File New Appeal – Medicare Operations Division” form. You are required to provide information and documents marked with an asterisk.

At a minimum, the Medicare Appeals Council requires an appellant to file a signed Request for Review and a copy of the enclosed decision. All documents should be submitted in Portable Document Format (PDF) whenever possible. Any document, including a Request for Review, will be deemed to have been filed on a given day, if it is uploaded to MOD E-File on or before 11:59 p.m. EST of that day.

Currently, the documents that may be filed electronically are the:

- (1) Request for Review;
- (2) Appointment of Representative form (OMB Form 0938-0950);
- (3) Copy of Administrative Law Judge or attorney adjudicator decision;
- (4) Memorandum or brief or other written statement in support of your appeal; and
- (5) Request to Withdraw your appeal

No other documents aside from the five (5) listed categories above may be submitted through MOD E-File.

Filing by oral request (for expedited review only):

Oral requests for expedited review of a Part D decision may be made by telephone to **(866) 365-8204**. You must provide the information listed in the bullet points above and a statement that you are requesting an expedited review within 60 calendar days after receipt of this notice of

decision. The Medicare Appeals Council will document the oral request in writing and maintain the documentation in the case file.

Please note that your request for review will only be expedited if (1) the appeal involves an issue specified in 42 C.F.R. § 423.566(b), but does not include solely a request for payment of a Part D drug that has already been furnished, and (2) the prescribing physician (or other prescriber) indicates, or the Medicare Appeals Council determines, that the standard time frame may seriously jeopardize your life, health, or ability to regain maximum function.

How will the Medicare Appeals Council respond to my appeal?

The Medicare Appeals Council will limit its review to the issues raised in the appeal, unless the appeal is filed by an unrepresented beneficiary/enrollee. It may change the parts of the decision that you agree with. It may adopt, modify, or reverse the decision, in whole or in part, or it may send the case back to OMHA for further action. It may also dismiss your appeal.

Questions?

You may call or write our office. A toll-free phone number and mailing address are at the top of this notice.

Additional information about filing an appeal with the Medicare Appeals Council is available at <http://www.hhs.gov/dab/>. You can also call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100 or (866) 365-8204 (toll free), if you have questions about filing an appeal.

cc:

DEBRA M PARRISH
788 WASHINGTON RD
PITTSBURGH, PA 15228

C2C Innovative Solutions, Inc.
DME QIC Appeals-ALJ
P.O. Box 44006
Jacksonville, FL 32231-4006

NOVOCURE INC.
195 Commerce Way
Portsmouth, NH 03801

Enclosures:

OMHA-152, Decision
OMHA-156, Exhibit List
DAB-101, Request for Review



**Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Miami, FL**

Appeal of: A. Prosser	ALJ Appeal No.: 1-8390277469
Beneficiary: A. Prosser	Medicare Part B
HICN: *****4857A	Before: J. Grow U.S. Administrative Law Judge

DECISION

After careful consideration of the entire record, an unfavorable decision is entered.

PROCEDURAL HISTORY

Claims were submitted to Medicare for an electrical stimulation device used for cancer treatment, HCPCS code E0766, dates of service 1/16/18, 2/16/18, 3/16/18, and 4/16/18. *See* Exh. 1 at 3. This type of treatment is also referred to as Tumor Treatment Field Therapy (TTFT). *Id.* These claims were denied, and Appellant filed an appeal which was denied upon redetermination and reconsideration. Exh. 1 at 13-16 and 1-7. At the reconsideration level, the Qualified Independent Contractor (QIC) listed the denial rationale as Local Coverage Determination L34823 (LCD L34823) requirements had not been met. Exh. 1 at 4. The QIC found the medical provider, and not the Appellant/Beneficiary (Appellant), liable for the non-covered charges. Exh. 1 at 5.

This matter involves a claim that meets the amount in controversy requirement, and the Appellant made a timely request for an Administrative Law Judge (ALJ) hearing before the Office of Medicare Hearings and Appeals (OMHA). *See* 42 C.F.R. § 405.1014(b)(1).

I held a telephone hearing on May 20, 2019. Debra M. Parrish, Esq., appeared for Appellant. Timothy Parks, Clinical Registered Nurse for the electrical stimulation device supplier, testified on Appellant's behalf. Exhibits 1 through 5 were admitted to the record without objection.

ISSUES

- A. Whether Medicare covers the electrical stimulation device/treatment, and
- B. If Medicare coverage is denied, then whether the waiver of liability provisions pursuant to § 1879 of the Social Security Act are applicable.

LEGAL FRAMEWORK

I. ALJ Review Authority

A. Jurisdiction

An individual or an organization that is dissatisfied with the reconsideration of an initial determination is entitled to a hearing before the Secretary of the Department of Health and Human Services (HHS), provided there is a sufficient amount in controversy and a request for hearing is filed in a timely manner. Social Security Act (Act) § 1869(b)(1)(A) (42 U.S.C. § 1395ff(b)(1)(A)).

In implementing this statutory directive, the Secretary has delegated the authority to administer the nationwide hearings and appeals system for the Medicare program to OMHA. *See* 70 Fed. Reg. 36386, 36387 (June 23, 2005). The ALJs within OMHA issue the final decisions of the Secretary, except for decisions the Medicare Appeals Council further review. *Id.*

In calendar year 2019, a hearing before an ALJ is only available if the remaining amount in controversy is \$160 or more for requests filed. *See* 83 Fed. Reg. 47619 (Sep. 20, 2018). A party to a QIC reconsideration may request a hearing before an ALJ if the party files a written request for an ALJ hearing within 60 days after receipt of the notice of the QIC's reconsideration. 42 C.F.R. § 405.1002(a).

B. Scope of Review

The issues before the ALJ include all the issues from the initial, reconsidered or revised determination that were not decided entirely in the Appellant's favor; however, if evidence presented before or during the hearing causes the ALJ to question a fully favorable decision, the Appellant will be notified and it will be considered an issue at hearing. 42 C.F.R. § 405.1032(a).

The ALJ may decide a case on the record and not conduct an oral hearing if the evidence in the hearing record supports a finding in favor of Appellant on every issue, or if the Appellant and all parties indicate in writing that they do not wish to appear before the ALJ at oral hearing. 42 C.F.R. § 405.1038.

The burden of proving each element of a Medicare claim lies with the Appellant by a preponderance of the evidence. *See* 42 C.F.R. §§ 424.5(a)(6), 405.1018, 405.1028, and 405.1030. All laws and regulations pertaining to the Medicare and Medicaid programs, including, but not limited to Titles XI, XVIII, and XIX of the Act and applicable implementing regulations, are binding on ALJ's. 42 C.F.R. § 405.1063.

An Appellant may offer new evidence for the first time at the ALJ level of appeal only upon a showing of good cause why the evidence was not submitted to the QIC or a prior decision maker. The ALJ will determine whether good cause exists for the late submission of the new evidence and may only consider the evidence in making a decision if good cause is found. *See* 42 C.F.R.

§§ 405.1018, 405.1028, and 405.1030. This new evidence restriction does not apply to unrepresented beneficiaries. *See* 42 C.F.R. § 405.1018(d).

Unless the ALJ dismisses the hearing request, the ALJ will issue a written decision that states findings of fact, conclusions of law, and the reasons for the decision. 42 C.F.R. § 405.1046(a). The decision must be based on evidence offered at the hearing or otherwise admitted into the record. *Id.*

C. Standard of Review

The ALJ conducts a *de novo* review of each claim at issue and issues a decision based on the hearing record. 42 C.F.R. § 405.1000(d). *De novo* review requires the ALJ to review and evaluate the evidence without regard to the findings of prior determinations on the claim and make an independent assessment relying upon the evidence and controlling laws.

II. Applicable Law

The Medicare program, Title XVIII of the Act, is administered through CMS, a component of HHS. The Secretary of HHS is authorized to enter into contracts with private entities for the administration of Part B of Title XVIII, the Supplementary Medical Insurance program, which provides coverage for a variety of medical services and supplies furnished by physicians, or by others in connection with physicians' services, for outpatient hospital services, and for a number of specific health-related items and services. *See* Act § 1842(a).

Part B beneficiaries participate voluntarily in the Medicare Part B program and pay a monthly premium. Part B entitles a beneficiary to have payments made on his or her behalf for "medical and other health services." Act § 1861(s)(3).

The items and services that are "not reasonable and necessary" for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member are specifically excluded from Medicare coverage. Act § 1862(a)(1)(A). Further, payment to any provider of services is precluded unless "there has been furnished such information as may be necessary in order to determine the amounts due such provider." Act § 1833(e) of the Act; *see* 42 C.F.R. § 424.5(a)(6).

The Act limits the liability of the beneficiary and providers of services if the services are found to be not medically reasonable and necessary under Section 1862(a)(1) of the Act or care was custodial in nature under Section 1862(a)(9) of the Act, and neither the beneficiary nor the provider knew or could reasonably have been expected to know that the services were not covered. Act § 1879; 42 U.S.C. § 1395pp; *see* 42 C.F.R. §§ 411.404, 411.406.

Unless promulgated as a regulation by CMS, no rule, requirement, or statement of policy, other than a National Coverage Determination (NCD), can establish or change a substantive legal standard governing the scope of benefits or payment for services under the Medicare program. However, in lieu of binding regulations with the full force and effect of law, CMS and its contractors have issued policy guidance that describe criteria for coverage of selected types of

medical items and services in the form of manuals and local medical review policies (LMRPs) or Local Coverage Determinations (LCDs). Act § 1871(a)(2)

The Act provides that ALJs will give substantial deference to LCDs, LMRPs or CMS program guidance when applicable, and if they do not follow the policy they must explain why in their decision. Act § Section 1869(f)(2); *see also* 42 CFR § 405.1062.

Specific to the instant case is Local Coverage Determination L34823, LCD for Tumor Treatment Field Therapy (effective 10/01/15), which was promulgated by CGS Administrators, LLC. It provides, in part: Tumor treatment field therapy (E0766) will be denied as not reasonable necessary.

The Medicare Appeals Council has cited LCD L34823 on several occasions in determining no Medicare TTFT coverage exists. *See* Medicare Appeals Council docket numbers M-19-1231 (April 23, 2019); M-19-755 (March 14, 2019); M-19-525 (March 14, 2019); and M-19-453 (March 8, 2019). Although these Council decisions are not precedential, they nonetheless represent HHS's final decision.

FINDINGS OF FACT AND ANALYSIS

- 1. Medicare does not cover the electrical stimulation device/treatment at issue because LCD L34823, which was in effect during the dates of service at issue, indicated there was no Medicare coverage for this device/treatment, and I must give LCDs substantial deference.*

The Appellant's attorney, Ms. Parrish, submitted a prehearing brief which discussed medical literature and professional medical societies which have determined that TTFT is safe and efficient. Exh. 4 at 6-7. Ms. Parrish's brief also discussed clinical trials which have shown TTFT to be safe and efficient. Ms. Parrish also emphasized in her brief that TTFT has been widely accepted by many major United States health coverage payors, as well as the fact that the Centers for Medicare Services previously assigned a HCPCS code with regard to TTFT devices. Exh. 4 at 8-8A. Finally, Ms. Parrish argued in her brief that LCD L34823 should not be given substantial deference due to several factors, including: "...the LCD's obvious failure to reflect the peer-reviewed literature, consensus of experts, and acceptance by the relevant medical community..." Exh. 4 at 8A.

At the hearing, Ms. Parrish emphasized that the Appellant was considered a "newly diagnosed" glioblastoma patient as of the dates of service at issue which were in 2016. She also discussed a favorable OMHA ALJ decision which had recently been issued with regard to different dates of service involving this same issue and this same Appellant. Ms. Parrish also indicated that medical contractors had proposed a new policy on May 9, 2019 which would allow Medicare TTFT coverage for newly diagnosed glioblastoma patients. According to Ms. Parrish, this had been preceded by a Medicare carrier advisory meeting which took place in early March 2019, following which the participants had recommended TTFT Medicare coverage for newly diagnosed glioblastoma patients. She also discussed a new proposed LCD which would provide TTFT coverage for newly diagnosed glioblastoma patients. According to Ms. Parrish, this new proposed LCD was in the public comment process as of the hearing date, May 20, 2019. Ms.

Parrish requested that I grant coverage for the Appellant here either by giving the current LCD substantial deference but refraining from applying the LCD or by taking the position that the evidence shows that the current LCD should only apply to “recurrent” glioblastoma patients and not to newly diagnosed glioblastoma patients.

Mr. Parks testified at the hearing regarding the Appellant’s clinical presentation and the various treatment modalities she had undergone since being diagnosed. He also discussed the differences between “newly diagnosed” glioblastoma and “recurrent” glioblastoma.

Although I find the Appellant’s arguments compelling, I also find the Appellant’s arguments amount to challenges to the underlying record upon which the LCD is based. A separate adjudicative process is available for aggrieved parties to challenge whether that LCD record is complete and adequate to support the validity of the LCD. *See* 42 C.F.R. 426.25 and Part 426 generally. I cannot make those types of findings here because I do not have the record upon which the LCD is based before me.

Given that LCD L34823 was in effect during the dates of service at issue and continues to remain in effect at the present time, I must substantially defer to the LCD and find no coverage.

2. *The provider, and not the Appellant, is responsible for the non-covered charges.*

The Act limits the liability of the Beneficiary and providers of items and services if the items and services are found to be not medically reasonable and necessary under Section 1862(a)(1) of the Act or care was custodial in nature under Section 1862(a)(9) of the Act, and neither the Beneficiary nor the provider knew or could reasonably have been expected to know that the items and services were not covered. Act § 1879; 42 U.S.C. § 1395pp; *see* 42 C.F.R. §§ 411.404, 411.406.

Medicare can reimburse for non-covered items and services if the provider or supplier of the items and services does not know, or have reason to know, that Medicare does not cover the items and services. The provider is a Medicare participant and must comply with all applicable laws and regulations. As a Medicare participant, the provider should be familiar with Medicare laws, regulations, and policies. The provider should have known the device and services that it provided to the Appellant are not covered by Medicare. The provider is therefore responsible for the non-covered charges.

The individual receiving the items and services is not liable for payment to the provider if the individual does not know, or have reason to know, that Medicare does not cover the items and services. There is no evidence in the record here indicating Appellant received advance notice, or knew, or should have known, that Medicare did not cover the item and service. Appellant is therefore not responsible for the non-covered charges.

CONCLUSIONS OF LAW AND ORDER

Medicare does not cover the item and services the Appellant received on the dates of service at issue. The Appellant is not liable to the provider for the item and services. The provider is not

eligible for coverage under § 1879 of the Act or Medicare regulations.

The Medicare contractor will process Appellant's claim in accordance with this decision.

Dated:

JUN 19 2019



J. Grow

U.S. Administrative Law Judge



**Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Miami, Florida**

Appeal of: **A. PROSSER**

OMHA Appeal No.: **1-8390277469**

Beneficiary: **A. PROSSER**

Medicare: **Part B**

Medicare No.: *******4857A**

Before: **J. Grow**
Administrative Law Judge

EXHIBIT LIST

EXHIBIT NUMBER	DESCRIPTION	PAGE NUMBERS
1	Initial, Redetermination and Reconsideration Procedural Documents	26
2	Medical Records/Evidence Received by CMS Contractors	243
3	Request for ALJ Hearing	11
4	OMHA Proceedings	24
5	Additional Evidence	30

Dated: **JUN 19 2019**

REQUEST FOR REVIEW OF ADMINISTRATIVE LAW JUDGE (ALJ) MEDICARE DECISION / DISMISSAL

1. APPELLANT (the party requesting review)	2. ALJ APPEAL NUMBER (on the decision or dismissal)
3. BENEFICIARY*	4. HEALTH INSURANCE CLAIM NUMBER (HICN)*

*If the request involves multiple claims or multiple beneficiaries, attach a list of beneficiaries, HICNs, or other information to identify all claims being appealed.

5. PROVIDER, PRACTITIONER, OR SUPPLIER	6. SPECIFIC ITEM(S) OR SERVICE(S)
--	-----------------------------------

7. Medicare claim type: ☐ Part A ☐ Part B ☐ Part C - Medicare Advantage
☐ Part D - Medicare Prescription Drug Plan ☐ Entitlement/enrollment for Part A or Part B

8. Does this request involve authorization for an item or service that has not yet been furnished?

☐ Yes If Yes, skip to Block 8.
☐ No If No, Specific Dates of Service:

9. If the request involves authorization for a prescription drug under Medicare Part D, would application of the standard appellate timeframe seriously jeopardize the beneficiary's life, health, or ability to regain maximum function (as documented by a physician) such that expedited review is appropriate? ☐ Yes ☐ No

I request that the Medicare Appeals Council review the ALJ's ☐ decision or ☐ dismissal order [check one] dated _____. I disagree with the ALJ's action because (specify the parts of the ALJ's decision or dismissal you disagree with and why you think the ALJ was wrong):

(Attach additional sheets if you need more space)

PLEASE ATTACH A COPY OF THE ALJ DECISION OR DISMISSAL ORDER YOU ARE APPEALING.

DATE			DATE		
APPELLANT'S SIGNATURE (the party requesting review)			REPRESENTATIVE'S SIGNATURE (include signed appointment if not already submitted.)		
PRINT NAME			PRINT NAME		
ADDRESS			ADDRESS		
CITY, STATE, ZIP CODE			CITY, STATE, ZIP CODE		
TELEPHONE NUMBER	FAX NUMBER	E-MAIL	TELEPHONE NUMBER	FAX NUMBER	E-MAIL

(SEE FURTHER INSTRUCTIONS ON PAGE 2)

If you have additional evidence, submit it with this request for review. If you need more time, you must request an extension of time in writing now, explaining why you are unable to submit the evidence or legal argument now.

If you are a provider, supplier, or a beneficiary represented by a provider or supplier, and your case was reconsidered by a Qualified Independent Contractor (QIC), the Medicare Appeals Council will not consider new evidence related to issues the QIC has already considered unless you show that you have a good reason for submitting it for the first time to the Medicare Appeals Council.

IMPORTANT: Include the HICN and ALJ Appeal Number on any letter or other material you submit.

This request must be received within 60 calendar days after you receive the ALJ's decision or dismissal, unless we extend the time limit for good cause. We assume you received the decision or dismissal 5 calendar days after it was issued, unless you show you received it later. If this request will not be received within 65 calendar days from the date on the decision or dismissal order, please explain why on a separate sheet.

You must file your request for review in writing with the Medicare Appeals Council at:

Department of Health and Human Services
Departmental Appeals Board
Medicare Appeals Council, MS 6127
Cohen Building Room G-644
330 Independence Ave., S.W.
Washington, D.C. 20201

You may send the request for review by U.S. Mail, a common carrier such as FedEx, or by fax to (202) 565-0227. If you send a fax, please do not also mail a copy. **You must send a copy of your appeal to the other parties and indicate that all parties, to include all beneficiaries, have been copied on the request for review. For claims involving multiple beneficiaries, you may submit a copy of the cover letters issued or a spreadsheet of the beneficiaries and addresses who received a copy of the request for review.**

If you have any questions about your request for review or wish to request expedited review of a claim involving authorization of your prescription drug under Medicare Part D, you may call the Medicare Appeals Council's staff in the Medicare Operations Division of the Departmental Appeals Board at (202) 565-0100. You may also visit our web site at www.hhs.gov/dab for additional information on how to file your request for review.

PRIVACY ACT STATEMENT

The collection of information on this form is authorized by the Social Security Act (section 205(a) of title II, section 702 of title VII, section 1155 of Title XI, and sections 1852(g)(5), 1869(b)(1), 1871, 1872, and 1876(c)(5)(B) of title XVIII, as appropriate). The information provided will be used to further document your claim. Information requested on this form is voluntary, but failure to provide all or any part of the requested information may affect the determination of your claim. Information you furnish on this form may be disclosed by the Department of Health and Human Services or the Social Security Administration to another person or governmental agency only with respect to programs under the Social Security Act and to comply with Federal laws requiring the disclosure of information or the exchange of information between the Department of Health and Human Services, the Social Security Administration, or other agencies.

January 18, 2019

**NOVOCURE, INC.
195 COMMERCE WAY
PORTSMOUTH, NH 03801**

Medicare Reconsideration Decision

RE:

Beneficiary: A. Prosser
Med ID#: *****4857A
Appellant: Novocure, Inc.

Dear S. Rice:

This letter is to inform you of the decision on your Medicare Appeal. An appeal is a new and independent review of a claim. You are receiving this letter because you requested an appeal for the services shown under the Appeal Details section.

The appeal decision is UNFAVORABLE. Our decision is that Medicare will make no additional payment. More information on the decision is provided on the next pages. You are not required to take any action.

If you disagree with the decision, you may appeal to an Administrative Law Judge (ALJ). You must file your appeal, in writing, within 60 days of receipt of this letter. For more information on how to appeal, see the page entitled "Important Information About Your Appeal Rights." The amount still in dispute is estimated to be equal to or over \$160.00. However, the ALJ will determine if your appeal case meets the \$160.00 amount in controversy requirement for an ALJ hearing.

**Contact
Information**

If you have
questions, write or
call:

***C2C Innovative
Solutions, Inc.***

QIC DME
P.O. Box 44163
Jacksonville, FL
32231-4163

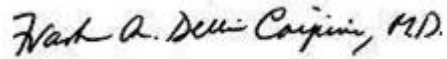
Telephone:
904-224-7433

Who we are:
We are a Qualified
Independent
Contractor (QIC).
Medicare has
contracted with us to
review your file and
make an independent
decision.

If this appeal is partially favorable or unfavorable,, and it originated from an overpayment, recoupment will begin 31 days from the date of this letter in the absence of an acceptable request for an extended repayment schedule (ERS). Please refer to the original demand letter for information regarding the collection process, interest accrual, and requesting an ERS.

A copy of this letter was also sent to the parties shown below. C2C Innovative Solutions, Inc. was contracted by Medicare to review your appeal. For more information on how to appeal, see the page titled "Important Information About Your Appeal Rights."

Sincerely,



Frank A. Delli Carpini, M.D.
Medical Director

CC: A. Prosser

Summary of Facts

The service(s) shown below were submitted for payment to CGS Administrators. The explanation of the decision was released in a Medicare Summary Notice to the beneficiary and a Remittance Advice to the provider of service. A request for a Redetermination appeal was submitted to the Medicare Administrative Contractor (MAC). On July 10, 2018, CGS Administrators completed the appeal and sent notice of the decision to the appropriate parties. On December 17, 2018, we received a QIC Reconsideration request for the services referenced in the "Appeal Details" section. Information and records reviewed by the QIC in this case included:

- Test Result(s)
- Redetermination Letter
- Proof of Delivery (POD)
- Physician Order/Prescription (RX)
- Medical Literature
- National or Local Coverage Determination (NCD or LCD) Medical Policy
- Request for Medical Records
- Treatment Record(s)
- Letter/Correspondence on behalf of beneficiary
- Supplier Delivery Documentation
- Reconsideration Request
- Beneficiary Letter/Correspondence
- Correspondence(s)

Decision

A panel of clinical experts consisting of a physician and a licensed health care professional reviewed the claim(s).

The decision on your appeal is shown below:

Medicare Coverage	Claim Number (ICN)	Procedure /Date of Service
Non-covered	18045802101000	E0766: Elec Stim Cancer Treatment - (01/16/18)
Non-covered	18050808224000	E0766: Elec Stim Cancer Treatment - (02/16/18)
Non-covered	18078813409000	E0766: Elec Stim Cancer Treatment - (03/16/18)
Non-covered	18107803853000	E0766: Elec Stim Cancer Treatment - (04/16/18)

We have determined that Novocure, Inc. is responsible for the denied charges.

Explanation of the Decision

Claim Number: 18045802101000

For any item or service to be covered by Medicare, it must fall into a defined Medicare benefit category, it must not be statutorily excluded, it must be reasonable and necessary under Section (§) 1862(a)(1)(A) of the Social Security Act (SSA), and it must meet other Medicare program requirements for payment. §§ 414.200 through 414.232 of 42 Code of Federal Regulations (CFR) cover payment for durable medical equipment and prosthetic and orthotic devices. The Medicare National Coverage Determinations (NCD) Manual, Publication 100-03, includes NCDs that pertain to certain Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS) items. The Medicare Claims Processing Manual, Publication 100-04, Chapter 20, instructs on billing and payment for DMEPOS. The Medicare Program Integrity Manual (PIM), Publication 100-08, Chapter 5, provides guidance on medical review. The manuals are based upon the above cited law and regulations. DME Medicare Administrative Contractors (MACs) publish Local Coverage Determinations (LCDs) and related Policy Articles. The LCDs address the criteria for "reasonable and necessary," based on Social Security Act § 1862(a)(1)(A). The articles encompass the non-medical necessity coverage and payment rules.

At issue is payment for an electrical stimulation device used for cancer treatment.

The Local Coverage Determination (LCD) for Tumor Treatment Field Therapy (TTFT) (L34823) states for any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. For the items addressed in this local coverage determination, the criteria for reasonable and necessary, based on Social Security Act § 1862(a)(1)(A) provisions, are defined by the coverage indications, limitations and/or medical necessity.

The Durable Medical Equipment (DME) Medicare Administrative Contractor (MAC) did not allow payment because the currently published studies in the medical literature did not clearly document the effectiveness of the device.

The DME Qualified Independent Contractor (QIC) performed an independent review. The available documentation submitted indicates the Beneficiary has a diagnosis of glioblastoma multiforme and is receiving TTFT treatment.

However, the currently published studies in the medical literature do not clearly document the effectiveness of this device, which is required as outlined in the LCD L34823. If the Novocure TTF is denied as not reasonable and necessary, the corresponding transducer arrays will be denied as not reasonable and necessary. Payment cannot be allowed. Based on the available documentation, the requirements of the LCD L34823 have not been met. Therefore, no payment can be allowed.

In conclusion, the decision of the DME QIC is unfavorable.

Claim Number: 18050808224000

Please see the complete decision under claim number 18045802101000.

Claim Number: 18078813409000

Please see the complete decision under claim number 18045802101000.

Claim Number: 18107803853000

Please see the complete decision under claim number 18045802101000.

Who is Responsible for the Bill?

When services are denied as not medically reasonable and necessary under the Medicare program, we must also determine if the provider or beneficiary is liable for payment. Section 1879(a)-(g) of the SSA, also referred to as "the limitation on liability provision," specifies how to arrive at this decision. Medicare regulations, 42 CFR 424, require providers to be familiar with Medicare rules and regulations. In addition, 42 CFR 411.406 provides criteria for determining when a provider is responsible for payment for the services considered not reasonable and necessary. This regulation states that providers are presumed to have knowledge of published Medicare coverage rules and regulations, Centers for Medicare and Medicaid Services (CMS) Rulings, Medicare coverage policies in CGS Administrators bulletins or websites, and acceptable standards within the local community. We find that Novocure Inc is liable for the denied charges. The record does not support that the beneficiary was notified in advance that Medicare would likely deny payment.

Other Important Information

If you appeal this decision, the Administrative Law Judge (ALJ) will not consider new evidence unless you show good cause for not presenting the evidence to the QIC. This requirement does not apply to beneficiaries, unless a provider or supplier represents the beneficiary.

For information on how to appeal this decision, refer to the page titled "Important Information About Your Appeal Rights." If you need more information or have any questions, please call 1-800-Medicare (1-800-633-4227) [TTY/TDD: 1-800-486-2048] or the phone number listed on page one.

You can receive copies of statutes, regulations, policies, and/or manual instructions we used to arrive at this decision. For instructions on how to do this, please see 'Other Important Information' on the page entitled "Important Information About Your Appeal Rights." The request must be submitted in writing to this office.

**Medicare Appeal
Number:**

1-8175102470

Appeal Details

Beneficiary	A. Prosser		
Provider	Novocure, Inc.		
Claim Number	Date of Service	Procedure	Medicare QIC Decision
18045802101000	01/16/18	E0766: Elec Stim Cancer Treatment	Unfavorable
18050808224000	02/16/18	E0766: Elec Stim Cancer Treatment	Unfavorable
18078813409000	03/16/18	E0766: Elec Stim Cancer Treatment	Unfavorable
18107803853000	04/16/18	E0766: Elec Stim Cancer Treatment	Unfavorable

THIS IS NOT A BILL – Keep this letter or a copy for your records.

IMPORTANT INFORMATION ABOUT YOUR APPEAL RIGHTS

Your Right to Appeal this Decision

If you do not agree with this decision, you may appeal the decision to an Administrative Law Judge (ALJ) at the Office of Medicare Hearings and Appeals (OMHA). The ALJ will review the decision to determine whether it is correct.

As of **January 1, 2018**, you must have **\$160.00** in dispute to appeal to an ALJ. A claim can be combined ("aggregated") with others to reach this amount if: (1) the other claims have also been decided or dismissed by a QIC; (2) all of the claims are listed on your request for review; (3) your request for review is filed within 60 days of receipt of all of the Qualified Independent Contractor (QIC) decisions being appealed; and (4) you explain why you believe the claims involve similar or related services. You can find more information about your right to an ALJ review of a QIC decision at www.hhs.gov/omha or by calling 1-855-556-8475. This is a toll free call.

How to Appeal

To exercise your right to appeal, you must file a written request for an ALJ review within **60 days** of receiving this letter. If your request for review is being filed late, you must explain why your request is being filed late. After you file an appeal, you may check your appeal's status via the OMHA website at www.hhs.gov/omha (click on Appeal Status Lookup).

When preparing your request for review, please use **Form OMHA-100**, available at:

www.hhs.gov/omha/forms/index.html

If you do not use the form, your request for review must include the following:

1. The Beneficiary's name, address, and Medicare health insurance claim number;
2. The name and address of the person appealing, if the person is not the beneficiary;
3. The representative's name and address, if any;
4. The Medicare appeal number listed on the front page of this Reconsideration notice;
5. The dates of service for the claims at issue;
6. The reasons why you disagree with the QIC's decision; and
7. A statement of any additional evidence to be submitted and the date it will be submitted.

You must send a copy of the request for ALJ review to the other parties who received a copy of this decision (for example, the beneficiary or provider/supplier). Please **do not** send a copy of your review request to the QIC that issued this decision or to the Medicare Administrative Contractor (MAC) that issued the Redetermination.

Mail your review request to (tracked mail is suggested):

HHS OMHA Central Operations
200 Public Square, Suite 1260
Cleveland, OH 44114-2316

OMHA processes Medicare **Beneficiary** appeals on a priority basis. If you are a Beneficiary or you represent a Beneficiary, mail your review request to:

HHS OMHA Central Operations
Attn: Beneficiary Mail Stop
200 Public Square, Suite 1260
Cleveland, OH 44114-2316

If you are a Beneficiary or represent a Beneficiary, you can also call the OMHA Beneficiary help line at 1-844-419-3358 for assistance. This is a toll free call. For more information on the OMHA Beneficiary prioritization program, including limitations for Beneficiaries represented by a provider/supplier, or a shared representative, visit the OMHA website at www.hhs.gov/omha or call the Beneficiary help line.

Who May File an Appeal

You or someone you name to act for you (your **appointed representative**) may file an appeal. You can name a relative, friend, advocate, attorney, doctor, or someone else to act for you.

If you want someone to act for you, you and your appointed representative must sign and date a statement naming that person to act for you and send it with your request for review. Call 1-800-MEDICARE (1-800-633-4227) to learn more about how to name a representative.

Help With Your Appeal

You can have a friend or someone else help you with your appeal. If you have any questions about payment denials or appeals, you can also contact your State Health Insurance Assistance Program (SHIP). For information on contacting your local SHIP, call 1-800-MEDICARE (1-800-633-4227).

Other Important Information

If you want copies of statutes, regulations, and/or policies we used to arrive at this dismissal, please write to us and attach a copy of this letter, at:

C2C Innovative Solutions, Inc.

A Medicare Contractor
P.O. Box 44163
Jacksonville FL 32231-4163

If you have questions, please call us at the phone number provided on the front of this notice.

Other Resources To Help You

1-800-MEDICARE (1-800-633-4227),
TTY/TDD: 1-800-486-2048

If you need large print or assistance, call 1-800-633-4227

January 18, 2019

**A. PROSSER
W2973 FARMSTEAD DRIVE
APPLETON, WI 54915-8120**

Medicare Reconsideration Decision

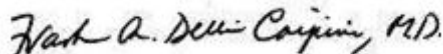
RE: Reconsideration Request
Reference attached chart for Appeal details

Dear A. Prosser:

Based on Medicare guidelines, you are entitled to a copy of our decision. Refer to the attached information for a description of the services that were at issue as well as our decision.

This notice is an informational copy for your records.

Sincerely,



Frank A. Delli Carpini, M.D.
Medical Director

Enclosure: Reconsideration decision

**Contact
Information**

If you have
questions, write or
call:

***C2C Innovative
Solutions, Inc.***

QIC DME
P.O. Box 44163
Jacksonville, FL
32231-4163

Telephone:
904-224-7433

Who we are:
We are a Qualified
Independent
Contractor (QIC).
Medicare has
contracted with us to
review your file and
make an independent
decision.

Summary of Facts

The service(s) shown below were submitted for payment to CGS Administrators . The explanation of the decision was released in a Medicare Summary Notice to the beneficiary and a Remittance Advice to the provider of service. A request for a Redetermination appeal was submitted to the Medicare contractor. On July 10, 2018, CGS Administrators completed the appeal, and sent notice of the decision to the appropriate parties. On December 17, 2018, we received a QIC Reconsideration request for the services referenced in the “Appeal Details” section. Information and records reviewed by the QIC in this case included:

- Test Result(s)
- Redetermination Letter
- Proof of Delivery (POD)
- Physician Order/Prescription (RX)
- Medical Literature
- National or Local Coverage Determination (NCD or LCD) Medical Policy
- Request for Medical Records
- Treatment Record(s)
- Letter/Correspondence on behalf of beneficiary
- Supplier Delivery Documentation
- Reconsideration Request
- Beneficiary Letter/Correspondence
- Correspondence(s)

Decision

A panel of clinical experts consisting of a physician and a licensed health care professional reviewed the claim(s).

The decision on your appeal is shown below:

Medicare Coverage	Claim Number (ICN)	Procedure /Date of Service
Non-covered	18045802101000	E0766: Elec Stim Cancer Treatment - (01/16/18)
Non-covered	18050808224000	E0766: Elec Stim Cancer Treatment - (02/16/18)
Non-covered	18078813409000	E0766: Elec Stim Cancer Treatment - (03/16/18)
Non-covered	18107803853000	E0766: Elec Stim Cancer Treatment - (04/16/18)

We have determined that Novocure, Inc. is responsible for the denied charges.

Explanation of the Decision

Claim Number:18045802101000

For any item or service to be covered by Medicare, it must fall into a defined Medicare benefit category, it must not be statutorily excluded, it must be reasonable and necessary under Section (§) 1862(a)(1)(A) of the Social Security Act (SSA), and it must meet other Medicare program requirements for payment. §§ 414.200 through 414.232 of 42 Code of Federal Regulations (CFR) cover payment for durable medical equipment and prosthetic and orthotic devices. The Medicare National Coverage Determinations (NCD) Manual, Publication 100-03, includes NCDs that pertain to certain Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS) items. The Medicare Claims Processing Manual, Publication 100-04, Chapter 20, instructs on billing and payment for DMEPOS. The Medicare Program Integrity Manual (PIM), Publication 100-08, Chapter 5, provides guidance on medical review. The manuals are based upon the above cited law and regulations. DME Medicare Administrative Contractors (MACs) publish Local Coverage Determinations (LCDs) and related Policy Articles. The LCDs address the criteria for "reasonable and necessary," based on Social Security Act § 1862(a)(1)(A). The articles encompass the non-medical necessity coverage and payment rules.

At issue is payment for an electrical stimulation device used for cancer treatment.

The Local Coverage Determination (LCD) for Tumor Treatment Field Therapy (TTFT) (L34823) states for any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. For the items addressed in this local coverage determination, the criteria for reasonable and necessary, based on Social Security Act § 1862(a)(1)(A) provisions, are defined by the coverage indications, limitations and/or medical necessity.

The Durable Medical Equipment (DME) Medicare Administrative Contractor (MAC) did not allow payment because the currently published studies in the medical literature did not clearly document the effectiveness of the device.

The DME Qualified Independent Contractor (QIC) performed an independent review. The available documentation submitted indicates the Beneficiary has a diagnosis of glioblastoma multiforme and is receiving TTFT treatment.

However, the currently published studies in the medical literature do not clearly document the effectiveness of this device, which is required as outlined in the LCD L34823. If the Novocure TTF is denied as not reasonable and necessary, the corresponding transducer arrays will be denied as not reasonable and necessary. Payment cannot be allowed. Based on the available documentation, the requirements of the LCD L34823 have not been met. Therefore, no payment can be allowed.

In conclusion, the decision of the DME QIC is unfavorable.

Claim Number:18050808224000

Revision Date

01272017

Please see the complete decision under claim number 18045802101000.

Claim Number:18078813409000

Please see the complete decision under claim number 18045802101000.

Claim Number:18107803853000

Please see the complete decision under claim number 18045802101000.

Who is Responsible for the Bill?

When services are denied as not medically reasonable and necessary under the Medicare program, we must also determine if the provider or beneficiary is liable for payment. Section 1879(a)-(g) of the SSA, also referred to as "the limitation on liability provision," specifies how to arrive at this decision. Medicare regulations, 42 CFR 424, require providers to be familiar with Medicare rules and regulations. In addition, 42 CFR 411.406 provides criteria for determining when a provider is responsible for payment for the services considered not reasonable and necessary. This regulation states that providers are presumed to have knowledge of published Medicare coverage rules and regulations, Centers for Medicare and Medicaid Services (CMS) Rulings, Medicare coverage policies in CGS Administrators bulletins or websites, and acceptable standards within the local community. We find that Novocure Inc is liable for the denied charges. The record does not support that the beneficiary was notified in advance that Medicare would likely deny payment.

Other Important Information

If you appeal this decision the Administrative Law Judge (ALJ) will not consider new evidence unless you show good cause for not presenting the evidence to the QIC. This requirement does not apply to beneficiaries, unless a provider or supplier represents the beneficiary.

For information on how to appeal this decision, refer to the page titled "Important Information About Your Appeal Rights." If you need more information or have any questions, please call 1-800-Medicare (1-800-633-4227) [TTY/TDD: 1-800-486-2048] or the phone number listed on page one.

You can receive copies of statutes, regulations, policies, and/or manual instructions we used to arrive at this decision. For instructions on how to do this, please see 'Other Important Information' on the page entitled "Important Information About Your Appeal Rights." The request must be submitted in writing to this office.

**Medicare Appeal
Number:**

1-8175102470

Appeal Details

Beneficiary	A. Prosser		
Provider	Novocure, Inc.		
Claim Number	Date of Service	Procedure	Medicare QIC Decision
18045802101000	01/16/18	E0766: Elec Stim Cancer Treatment	Unfavorable
18050808224000	02/16/18	E0766: Elec Stim Cancer Treatment	Unfavorable
18078813409000	03/16/18	E0766: Elec Stim Cancer Treatment	Unfavorable
18107803853000	04/16/18	E0766: Elec Stim Cancer Treatment	Unfavorable

THIS IS NOT A BILL – Keep this letter or a copy for your records.

Revision Date

01272017

IMPORTANT INFORMATION ABOUT YOUR APPEAL RIGHTS

Your Right to Appeal this Decision

If you do not agree with this decision, you may appeal the decision to an Administrative Law Judge (ALJ) at the Office of Medicare Hearings and Appeals (OMHA). The ALJ will review the decision to determine whether it is correct.

As of January 1, 2018, you must have \$160.00 in dispute to appeal to an ALJ. A claim can be combined ("aggregated") with others to reach this amount if: (1) the other claims have also been decided or dismissed by a QIC; (2) all of the claims are listed on your request for review; (3) your request for review is filed within 60 days of receipt of all of the QIC dismissals being appealed; and (4) you explain why you believe the claims involve similar or related services.

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When preparing your request for review, please use **Form OMHA-100**, available at:

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1. The Beneficiary's name, address, and Medicare health insurance claim number;
2. The name and address of the person appealing, if the person is not the beneficiary;
3. The representative's name and address, if any;
4. The Medicare appeal number listed on the front page of this Reconsideration notice;
5. The dates of service for the claims at issue;
6. The reasons why you disagree with the QIC's dismissal; and
7. A statement of any additional evidence to be submitted and the date it will be submitted.

You must send a copy of the request for ALJ review to the other parties who received a copy of this decision (for example, the beneficiary or provider/supplier). Please **do not** send a copy of your review request to the QIC that issued this decision or to the Medicare Administrative Contractor that issued the Redetermination.

Mail your review request to (tracked mail is suggested):

HHS OMHA Central Operations
200 Public Square, Suite 1260
Cleveland, OH 44114-2316

OMHA processes Medicare **Beneficiary** appeals on a priority basis. If you are a Beneficiary or you represent a Beneficiary, mail your review request to:

HHS OMHA Central Operations
Attn: Beneficiary Mail Stop
200 Public Square, Suite 1260
Cleveland, OH 44114-2316

If you are a Beneficiary or represent a Beneficiary, you can also call the OMHA Beneficiary help line at 1-844-419-3358 for assistance. This is a toll free call. For more information on the OMHA Beneficiary prioritization program, including limitations for Beneficiaries represented by a provider/supplier, or a shared representative, visit the OMHA website at www.hhs.gov/omha or call the Beneficiary help line.

Who May File an Appeal

You or someone you name to act for you (your **appointed representative**) may file an appeal. You can name a relative, friend, advocate, attorney, doctor, or someone else to act for you.

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Help With Your Appeal

You can have a friend or someone else help you with your appeal. If you have any questions about payment denials or appeals, you can also contact your State Health Insurance Assistance Program (SHIP). For information on contacting your local SHIP, call 1-800-MEDICARE (1-800-633-4227).

Other Important Information

If you want copies of statutes, regulations, and/or policies we used to arrive at this dismissal, please write to us and attach a copy of this letter, at:

C2C Innovative Solutions, Inc.

A Medicare Contractor
P.O. Box 44163
Jacksonville FL 32231-4163

If you have questions, please call us at the phone number provided on the front of this notice.

Other Resources To Help You

1-800-MEDICARE (1-800-633-4227),
TTY/TDD: 1-800-486-2048

If you need large print or assistance, call 1-800-633-4227

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF MEDICARE HEARING AND APPEALS
DEPARTMENTAL APPEALS BOARD
MEDICARE OPERATIONS DIVISION

In the Matter of:

ANNIKEN PROSSER,

Appellant,

v.

**CENTERS FOR MEDICARE & MEDICAID
SERVICES,**

Respondent.

Appeal No. **1-8390277469**

The above-entitled matter came on for hearing pursuant to notice before **JOSEPH GROW**, Administrative Law Judge, at the **Office of Medicare Hearings and Appeals, Miami, Florida**, on **Monday, May 20, 2019**, at **2:00 p.m.**

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

A P P E A R A N C E S

On Behalf of the Appellant:

DEBRA PARRISH, Attorney
Parrish Law offices

On Behalf of the Respondent:

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

I N D E X

<u>WITNESS</u>	<u>DIRECT</u>	<u>CROSS</u>	<u>REDIRECT</u>	<u>RECROSS</u>
Timothy Parks	6	--	--	--

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

E X H I B I T SEXHIBITSFOR IDENTIFICATIONIN EVIDENCE

Exhibits

2

2

1

P R O C E E D I N G S

2

(Time Noted: 2:00 p.m.)

3

JUDGE GROW: Good afternoon. Today is May 20th, 2019.

4

The time is 2 p.m. Eastern Time. I'm Administrative Law Judge

5

Joseph Grow with the Office of Medicare Hearings and Appeals.

6

Today I am hearing an appeal claim from the beneficiary,

7

Ms. Anniken Prosser. This is ALJ Appeal Number 1-8390277469.

8

I am making a digital recording of this hearing. It will

9

be made part of the complete record. It is a de novo hearing,

10

meaning I'm not bound by any prior determinations made in this

11

matter. The burden of proof is on the Appellant by a

12

preponderance of the evidence.

13

On the phone line with me, I have Ms. Debra Parrish,

14

representing the beneficiary. She is an attorney.

15

Can you hear me okay, Ms. Parrish?

16

MS. PARRISH: I Can, Your Honor.

17

JUDGE GROW: Thank you.

18

Also, her witness is Mr. Timothy Parks.

19

Mr. Parks, do you want to briefly introduce yourself for

20

the record, and state your title, and your degrees and

21

certifications that may be relevant?

22

MS. PARRISH: Absolutely, Your Honor. My name is Timothy

23

Parks. I am a registered nurse with a BSN. I am a published

24

research author pertaining to anti-cancer medicine. And I am a

25

clinical field specialist here at Novocure. Yes.

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1 JUDGE GROW: Okay.

2 **(Witness sworn.)**

3 JUDGE GROW: All right, thank you. The issue that I'll
4 decide in this case is whether Medicare covers the tumor
5 treatment field therapy provided to Ms. Prosser on four dates
6 of service, January 16th, 2018, February 16th, 2018, March
7 16th, 2018 and April 16th, 2018.

8 If I do find that Medicare does not cover those medical
9 services, I'll determine -- or items, I'll determine who may be
10 responsible for any noncovered charges.

11 Any objection to the issue, Ms. Parrish?

12 MS. PARRISH: No, Your Honor. No objection.

13 JUDGE GROW: Okay. I want to speak about exhibits. I
14 have marked documents that I would like to enter into the
15 record. These include the prior determinations made in this
16 matter, evidence received from the government contractors
17 relating to those determinations, the request for hearing, the
18 notice of hearing, and the responses to the notice of hearing.

19 Any objections to me entering these documents into
20 evidence, Ms. Parrish?

21 MS. PARRISH: No objection, Your Honor.

22 JUDGE GROW: All right, thank you.

23 **(Hearing exhibits marked for identification and received into**
24 **evidence.)**

25 JUDGE GROW: I've gone through the record, and I also --

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1 and then received with the response to the notice of hearing of
2 your prehearing brief, I've gone through that. And this is
3 your opportunity to make any arguments you'd like to make,
4 point me to any specific evidence you want me to consider.

5 I know you briefly explained something to me off the
6 record. I think you want to, maybe you talk about that on the
7 record now at this time. So when you're ready, you may
8 proceed. And then we can also question Mr. Parks as you wish.

9 MS. PARRISH: Thank Your Honor. As we know, unfortunately
10 Ms. Prosser was diagnosed with a -- newly diagnosed with a
11 glioblastoma. She is extremely young, a 35-year-old mother
12 with a young child, and was -- consistent with the standard of
13 care, had surgery and chemoradiation. And then also,
14 consistent with the standard of care, she was prescribed with
15 this device.

16 As you saw, the QIC denied it, stating that the medical
17 documentation is not within the scope and breadth of the
18 literature, and made some other statements about whether the
19 studies were sufficient in number or, and not nonbiased. I
20 think that's the word they kind of used.

21 And I address all of that essentially in my prehearing
22 brief. But probably two things that are relevant that I did
23 not discuss in the prehearings -- three things that are
24 relevant.

25 First, I wanted to make sure you understood that although

1 she was diagnosed in 2016, in fact, Ms. Prosser is considered
2 newly diagnosed because she has not had a progression. And in
3 fact, her RMIs show that she's actually had a regression. But
4 I'm sure Mr. Parks will speak to her diagnosis, and the
5 actually fabulous results that she has had with this treatment.

6 Second, I did make you aware, offline, that today we
7 received a favorable decision for other dates of service for
8 Ms. Prosser for the same device, for the same condition.

9 And then finally, probably most importantly, I believe
10 that it addresses many of the issues raised. On May 9th, the
11 Medicare contractors proposed a new policy for newly diagnosed
12 glioblastoma. And as you saw, I pointed out in the prehearing
13 brief that they did produce the LCD record for the current LCD
14 that was studied in the decision. And in fact, it shows that
15 they stopped considering any of the literature or any of the
16 clinical or scientific developments that occurred after 2014.

17 And I also made you aware that they convened a Medicare
18 Advisory Committee meeting. They met at the beginning of March
19 of this year, and that recommended coverage. And then May 9th,
20 we actually had the LCD issue, which I will be happy to submit
21 to you, which states that it will cover tumor treatment field
22 therapy for individuals who've been newly diagnosed with a
23 glioblastoma. So they would extend coverage to individuals
24 such as Ms. Prosser. And in that, they cite, as the basis for
25 that, the *JAMA* 2017 article.

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1 They did not yet give an effective date of it, but in my
2 experience, often if an LCD is supported by literature -- and
3 you see this most often with laboratory tests, where they
4 submit dossier, the based upon when the evidence was sufficient
5 as that's when they might make the effective date retroactive
6 to.

7 So I don't know what they will do. But be that as it may,
8 given in the LCD, they specifically cited to 2017 dates of
9 service, and we're here on 2018 dates of service, and by 2018,
10 every major payer in our country was covering it, all the
11 regional ones, it was included in the -- as a standard of care
12 in the NCCN guidelines, and there was widespread adoption
13 throughout the entire United States, I expect that they would
14 find that all of the elements are supported, for Medicare
15 coverage are supported. You have the literature, consensus of
16 experts, and widespread adoption.

17 The comment period for that draft LCD does not end,
18 unfortunately, until June 24th. And as Your Honor may be
19 aware, they have, a lot of times and too, are now required now
20 to address all the comments submitted as part of the LCD. So
21 although we're coming to the end of that process, I don't
22 anticipate they will actually have a finalized LCD in a timely
23 manner.

24 So I believe this case should appropriately adjudicate it.
25 You can either give substantial deference to the LCD but not

1 apply it, in view of the most current analysis of the
2 information, which addresses newly diagnosed as opposed to the
3 prior, which only sets the information with respect to
4 recurrence. Or you can take the position that the DME MAC
5 medical directors did, whether I agree with it or not, saying
6 that the LCD did not apply to newly-diagnosed glioblastoma, in
7 which case you are forced into the analysis of the same
8 criteria, the literature, consensus of experts and whether it's
9 widely accepted by the relevant medical community.

10 So I believe that she meets Medicare coverage for tumor
11 treatment field therapy for the dates of service at issue.

12 (Whereupon,

13

TIMOTHY PARKS

14 was called as a witness and, after having been first duly
15 sworn, was examined and testified as follows:)

16

DIRECT EXAMINATION

17 Q. BY MS. PARRISH: And with that, I would ask, Mr. Parks,
18 could you just briefly review Ms. Prosser's clinical
19 presentation?

20 A. Yes, thank you. Ms. Prosser was, originally started to
21 notice some headaches and some neurological changes in the
22 beginning of 2016, February. They performed an MRI on February
23 14th, 2016. And the MRI showed a left temporal mass, which is
24 supratentorial, a mass in her brain. The tumor was surgically
25 resected on February 26th, 2016, and the pathology report

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1 confirmed that it was glioblastoma.

2 After the surgery, they -- she completed the standard
3 course of chemoradiation therapy, followed by monthly
4 temozolomide and Optune therapy, which started June 16th, 2016,
5 which is less than 7 weeks after she completed the
6 chemoradiation therapy.

7 Her MRIs remained stable throughout the treatment, and she
8 completed the temozolomide on April 12th of 2017, so a year, a
9 standard 12 months of temozolomide. After that, she was on
10 Optune alone, and again, her MRIs, March, September, December
11 of 2018 all remained stable, even on the -- I would even go as
12 far as saying on December 19th of 2018, that the MRI states
13 that the tumor has actually shrunk. And that's with using
14 Optune alone. And then March 19th, 2019, April 10th, 2019, all
15 MRIs have remained stable.

16 She has a KPS score of 80 percent and an ECOG score of 0.
17 And she uses the device almost like 90 percent of the time,
18 which -- you know, technically it says that it's supposed to be
19 75 percent in the new LCD, but she uses it more than that.

20 MS. PARRISH: Your Honor, do you have any questions for
21 Mr. Parks about her clinical presentation?

22 JUDGE GROW: I just had some -- do you want to talk maybe
23 a little bit about the -- this is considered a newly-diagnosed
24 glioblastoma?

25 MS. PARRISH: Sure.

1 THE WITNESS: Yeah. I could do that if you like,
2 Ms. Parrish.

3 Q. BY MS. PARRISH: Sure. Yes, please.

4 A. Okay. So, basically how glioblastoma works is it's an
5 orphan disease, so like Ms. Parrish said, it starts in the
6 brain, and it doesn't start anywhere else. It's just there.
7 Once they discover the tumor, it's considered newly diagnosed.

8 Once they do treatment, surgery and chemoradiation, which
9 is the gold standard, then they -- it's still considered newly.
10 And so once they complete that treatment, if for some reason
11 the doctors or MRI conclude that there was a progression, or a
12 recurrence, as they call it, that patient is then considered
13 recurrent.

14 But if the tumor has -- they have the treatment for the
15 chemoradiation therapy and the surgery, and then whatever other
16 treatments they're going to do, which is basically Optune, then
17 the patient remains newly. So they will remain newly until
18 there's a progression. And this patient has not had a
19 progression in that MRI.

20 JUDGE GROW: All right, so I'm not sure I understand. So
21 she was diagnosed in 2016.

22 THE WITNESS: Yes.

23 MS. PARRISH: She's still considered new.

24 JUDGE GROW: All right.

25 MS. PARRISH: She has not -- because she has not had a

1 progression, she's still considered newly diagnosed. Unless
2 and until you have a progression, you're considered newly
3 diagnosed.

4 JUDGE GROW: Yeah.

5 MS. PARRISH: So she hasn't had one.

6 JUDGE GROW: Okay. You referenced the -- the LCD record
7 was produced, I guess, in the legal proceeding under -- are you
8 challenging this LCD under --

9 MS. PARRISH: Yes.

10 JUDGE GROW: -- 42 C.F.R. Part 426?

11 MS. PARRISH: Yes.

12 JUDGE GROW: Okay.

13 MS. PARRISH: And -- go ahead.

14 JUDGE GROW: And then, where is that? Has that been
15 decided yet?

16 MS. PARRISH: One time question, Your Honor. So, the LCD
17 challenge was filed. It was deemed to be a valid challenge.
18 The AP statement was filed last Thursday when they filed the
19 draft LCD. They moved -- actually it was the 9th, so it wasn't
20 last Thursday, excuse me. Ten days, so whatever -- eleven.
21 They moved to have it dismissed in view of the anticipated
22 coverage. That motion to dismiss was denied.

23 Today is the day they are supposed to indicate whether
24 they think the information submitted with the aggrieved party
25 statement was significant, identify any witnesses they intend

1 to call, and identify whether they intend to cross-examine any
2 of the witnesses that we offered. And there was a third,
3 another thing that they needed to do, you know, file their
4 response. And a hearing is set for June 24th, if the judge
5 determines that a hearing is necessary. So today is the day of
6 their response.

7 JUDGE GROW: Okay. Now I don't have the proposed LCD, so
8 do you want to fax that in to me?

9 MS. PARRISH: Sure. What's the best number, Your Honor,
10 to fax that to? Just the one on your papers, the normal one?
11 There's not a special one?

12 JUDGE GROW: Right. It's the 305-536-5044.

13 MS. PARRISH: Okay. I'll do that one.

14 JUDGE GROW: Okay. And you're able to maybe send that
15 over today or tomorrow?

16 MS. PARRISH: Oh, I'll do it right after we hang up here.

17 JUDGE GROW: Okay, perfect.

18 MS. PARRISH: I have lots of copies here.

19 JUDGE GROW: Well perfect. And then you have an ALJ
20 decision -- was it a ALJ decision that granted --

21 MS. PARRISH: Literally, it granted coverage. It
22 literally just arrived this morning with like the 10 a.m. mail
23 or I would have sent it earlier.

24 JUDGE GROW: Okay. So you want to send that over now,
25 with that other?

1 MS. PARRISH: Sure. I'll do that as well. Yeah.

2 JUDGE GROW: Okay. And I know, in the information
3 submitted there was all these ALJ decisions that did allow
4 coverage for some more --

5 MS. PARRISH: Situations, yeah.

6 JUDGE GROW: Yeah, situation. Right. Has this -- I know
7 it's been up to the --

8 MS. PARRISH: Council?

9 JUDGE GROW: -- Council at least a couple times. What's
10 going on with these other cases? Are some of them becoming
11 finalized? Or are they all being appealed up to the Council?

12 MS. PARRISH: So, if there's just a -- sure. And again,
13 I'm not -- I'm just putting this right out here. I am not the
14 only game in town. But I'm just going to say, on the cases
15 where I represent the beneficiary -- and all I do is
16 beneficiary appeals, when I represent the beneficiary, if it's
17 unfavorable, and the beneficiary is still alive, and I hate to
18 say it that way, but it's, it is how it is, I appeal them to
19 the Medicare Appeals Council.

20 One decision issued on a Part C plan, I believe, either
21 one or two maybe issued, saying that an ALJ was bound by the
22 LCD in a Part C case. I anticipate taking that case further
23 because I think it's contrary to the statute and regulations.
24 But other than that, on the cases where I have represented a
25 beneficiary, we do not have a final decision. If that's your

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1 question to me.

2 JUDGE GROW: You don't have a final decision, meaning the
3 Council hasn't --

4 MS. PARRISH: From the Council.

5 JUDGE GROW: -- issued that?

6 MS. PARRISH: From the Council. One of the old -- I
7 actually got a communication today on one of the older cases,
8 but they have not issued a decision. They just -- there was
9 something else happening in that case they asked for my input
10 on. That's all. But no, if you're asking me my question, no,
11 they -- yeah, I only have that decision about Part C, the LCD
12 being binding on an ALJ, if that's your question.

13 JUDGE GROW: Okay. What --

14 MS. PARRISH: I think -- go ahead.

15 JUDGE GROW: Well no, no. I just -- I'm -- out of
16 curiosity, it's -- when there's a Part C plan and there's an
17 LCD, I think there's a regulation that says the Part C plan, at
18 that level, can't stray from the LCD, I believe. Is that where
19 you --

20 MS. PARRISH: Right. So there's -- it's a two-part
21 question. So, you're a hundred percent correct that the LCD is
22 binding -- well, it's not binding, but they have to at least
23 cover things that are the subject of an LCD. The Medicare
24 Advantage plan can cover more than the original Medicare
25 coverage, but they have to follow an LCD that extends coverage.

1 And as I'm sure, so the Medicare Advantage plans, a number
2 of them have followed that LCD despite that August 2018
3 communication. But when it gets to your level, I think the
4 statute and regulations are clear that the LCD is not binding
5 on an ALJ at this level in a Part C plan, any more than an ALJ
6 is bound by an LCD for original Medicare. It's the same
7 scenario, right.

8 JUDGE GROW: Okay.

9 MS. PARRISH: So, I can't be CDS. And for, you know,
10 John, I say, well I'm not going to apply my LCD for John. But
11 for Jane, I am going to apply my -- it's to have the
12 consistency at the contractor and plan level. But when you get
13 to the ALJ level, you're allowed to consider all of these other
14 factors. There is, though, as I shared with you, a council
15 decision saying, because the plan is bound to follow its LCD,
16 they have interpreted to say that the ALJ is bound. And I
17 think that's contrary to the statute and regulations, which
18 specifically says --

19 JUDGE GROW: Okay.

20 MS. PARRISH: -- everybody gets a de novo at ALJ, not
21 binding. If that's your question.

22 JUDGE GROW: Yes, yes. Thank you for that clarification.
23 Okay, so I will look for the new evidence. I'll admit that
24 into the record.

25 MS. PARRISH: Sure.

1 JUDGE GROW: And I'll make my decision shortly thereafter,
2 in writing. And that should be coming out no later -- leaving
3 the office no later than June 20th.

4 Any questions about anything, or anything further?

5 MS. PARRISH: No. I think the -- I think that's it, Your
6 Honor. I think those are the salient points for Ms. Prosser.
7 She's a fairly young woman, so I'm hoping that she will have
8 coverage.

9 JUDGE GROW: All right. Well thank you so much to both of
10 you for taking the time and explaining your position and for
11 testifying today. And we will be in touch shortly.

12 MS. PARRISH: Thank you so much, Your Honor.

13 JUDGE GROW: All right, thank you.

14 MR. PARKS: Thank you, Your Honor.

15 MS. PARRISH: Bye.

16 JUDGE GROW: Bye.

17 **(Whereupon, the hearing in the above-entitled matter was**
18 **adjourned.)**

19

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CERTIFICATION

This is to certify that the attached proceedings before the Office of Medicare Hearings and Appeals, in the matter of **ANNIKEN PROSSER v. CENTERS FOR MEDICARE AND MEDICAID SERVICES**, Appeal No. 1-8390277469, convened at Miami, Florida on May 20, 2019, before Joseph Grow, Administrative Law Judge, were held and recorded as herein appears, and that this is the original, complete, true and accurate transcript that has been compared to the reporting or recording accomplished at the hearing.



Pamela C. Jacobson
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